EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1501	((546/335) or (546/269.7)).CCLS.	US-PGPUB; USPAT	OR	OFF	2007/09/24 23:42
L2	105	1 and pioglitazone	US-PGPUB; USPAT	OR	OFF	2007/09/24 23:42
L3	77	1 and pioglitazone and intermediate	US-PGPUB; USPAT	OR	OFF	2007/09/24 23:42

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PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

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NEWS 1		Web Page for STN Seminar Schedule - N. America
NEWS 2	JUL 02	LMEDLINE coverage updated
NEWS 3	JUL 02	SCISEARCH enhanced with complete author names
NEWS 4	JUL 02	CHEMCATS accession numbers revised
NEWS 5	JUL 02	CA/CAplus enhanced with utility model patents from China
NEWS 6	JUL 16	CAplus enhanced with French and German abstracts
NEWS 7	JUL 18	CA/CAplus patent coverage enhanced
NEWS 8	JUL 26	USPATFULL/USPAT2 enhanced with IPC reclassification
NEWS 9	JUL 30	USGENE now available on STN
NEWS 10	AUG 06	CAS REGISTRY enhanced with new experimental property tags
NEWS 11	AUG 06	BEILSTEIN updated with new compounds
NEWS 12	AUG 06	FSTA enhanced with new thesaurus edition
NEWS 13	AUG 13	CA/CAplus enhanced with additional kind codes for granted patents
NEWS 14	AUG 20	CA/CAplus enhanced with CAS indexing in pre-1907 records
NEWS 15	AUG 27	Full-text patent databases enhanced with predefined patent family display formats from INPADOCDB
NEWS 16	AUG 27	USPATOLD now available on STN
NEWS 17	AUG 28	CAS REGISTRY enhanced with additional experimental spectral property data
NEWS 18	SEP 07	STN AnaVist, Version 2.0, now available with Derwent World Patents Index
NEWS 19	SEP 13	FORIS renamed to SOFIS
NEWS 20	SEP 13	INPADOCDB enhanced with monthly SDI frequency
NEWS 21	SEP 17	CA/CAplus enhanced with printed CA page images from 1967-1998
NEWS 22	SEP 17	CAplus coverage extended to include traditional medicine patents
NEWS 23	SEP 24	EMBASE, EMBAL, and LEMBASE reloaded with enhancements

NEWS EXPRESS 19 SEPTEMBER 2007: CURRENT WINDOWS VERSION IS V8.2, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 19 SEPTEMBER 2007.

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
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Updated Search

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FILE 'HOME' ENTERED AT 21:58:30 ON 24 SEP 2007

=> file reg
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

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STRUCTURE FILE UPDATES:   23 SEP 2007  HIGHEST RN 947726-74-1
DICTIONARY FILE UPDATES:  23 SEP 2007  HIGHEST RN 947726-74-1

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http://www.cas.org/support/stngen/stndoc/properties.html

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L1      STRUCTURE UPLOADED

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SAMPLE SCREEN SEARCH COMPLETED -     4311 TO ITERATE

 46.4% PROCESSED     2000 ITERATIONS                                 2 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:        82283 TO    90157
PROJECTED ANSWERS:               2 TO      210

L2            2 SEA SSS SAM L1

=> s l1 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 171.65 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 22:03:23 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    86500 TO ITERATE


Updated Search
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100.0% PROCESSED 86500 ITERATIONS 35 ANSWERS
SEARCH TIME: 00.00.01

L3 35 SEA SSS FUL L1

=> file hcaplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 175.25 175.46

FILE 'HCAPLUS' ENTERED AT 22:03:28 ON 24 SEP 2007
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FILE COVERS 1907 - 24 Sep 2007 VOL 147 ISS 14
FILE LAST UPDATED: 23 Sep 2007 (20070923/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3
L4 17 L3

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168 BOYER, F?/AU
L6 0 L4 AND BOYER, F?/AU

=> s l4 and hagen, s?/au
363 HAGEN, S?/AU
L7 0 L4 AND HAGEN, S?/AU

=> s l4 and kaneko, t?/au
6847 KANEKO, T?/AU
L8 0 L4 AND KANEKO, T?/AU

=> s l4 and lall, m?/au
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L9 0 L4 AND LALL, M?/AU

=> s 4 and pettersson, m?/au
5677402 4
168 PETTERSSON, M?/AU

Updated Search

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=> s l4 and prasad, j?/au
            808 PRASAD, J?/AU
L13           0 L4 AND PRASAD, J?/AU

=> d l4, ibib abs hitstr, 1-17

L4   ANSWER 1 OF 17  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2007:183978  HCAPLUS
DOCUMENT NUMBER:          146:417429
TITLE:                    Synthesis and Binding Affinity of a
                          Fluorine-Substituted Peroxisome Proliferator-Activated
                          Gamma (PPARγ) Ligand as a Potential Positron
                          Emission Tomography (PET) Imaging Agent
AUTHOR(S):                Lee, Byung Chul; Lee, Kyo Chul; Lee, Hsiaoju; Mach,
                          Robert H.; Katzenellenbogen, John A.
CORPORATE SOURCE:         Department of Chemistry, University of Illinois,
                          Urbana, IL, 61801, USA
SOURCE:                   Bioconjugate Chemistry (2007), 18(2), 507-513
                          CODEN: BCCHES; ISSN: 1043-1802
PUBLISHER:                American Chemical Society
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   The peroxisome proliferator-activated receptor γ (PPARγ) is an
     important regulator of lipid metabolism and the differentiation of
     pre-adipocytes.  Thus, imaging PPARγ in vivo using positron-emission
     tomog. (PET) might be useful in assessing lipid metabolism disorders and
     identifying tumor cell differentiation.  A fluorine-substituted
     PPARγ ligand from tyrosine-benzophenone class, compound 1, has a very
     high affinity for PPARγ receptor (Ki = 0.14 nM).  To develop this
     compound as a PPARγ PET imaging agent, we investigated synthetic
     routes suitable for its labeling with the short-lived PET radionuclide
     fluorine-18 (t1/2 = 110 min).  To obtain the high specific activity
     material needed for receptor imaging with this isotope, reactions need to
     proceed efficiently, within a short time, starting from fluoride ion at
     the tracer level.  The most promising approach involves introduction of
     fluorine into a suitable benzophenone precursor, followed by efficient
     coupling of this intermediate with the heterocyclic tyrosine component
     using a copper-catalyzed Ullmann-type condensation.
IT   258347-27-2P
     RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
     (Reactant or reagent)
        (preparation and binding affinity of fluorine-substituted PPARγ ligand
        as potential PET imaging agent)
RN   258347-27-2  HCAPLUS
CN   L-Tyrosine, O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]-,
     2,2,2-trifluoroacetate (1:1)  (CA INDEX NAME)

     CM   1

     CRN  185679-35-0
     CMF  C21 H22 N2 O4


Updated Search
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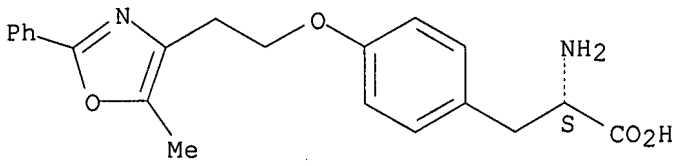
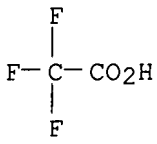
Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

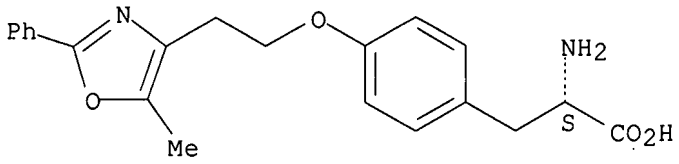


REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:1342501 HCAPLUS
DOCUMENT NUMBER: 145:397748
TITLE: Improved synthesis of a new antidiabetic agent, GW409544
AUTHOR(S): Zhou, Xinbo; Lin, Cuifang; Li, Song
CORPORATE SOURCE: School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Shenyang, Liaoning Province, 110016, Peop. Rep. China
SOURCE: Zhongguo Yaowu Huaxue Zazhi (2005), 15(3), 167-169
CODEN: ZYHZEF; ISSN: 1005-0108
PUBLISHER: Zhongguo Yaowu Huaxue Zazhi Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
OTHER SOURCE(S): CASREACT 145:397748
AB The synthesis of GW409544 was reported. GW409544 was synthesized by using Me 3-oxopentanoate and L-tyrosine as the starting material via nine steps, such as esterification, amino protection, bromination, cyclization, reduction, etherification, deprotection, hydrolysis, condensation and salt formation, etc. The target compound was identified by spectroscopic anal., and the overall yield was 9.3%. The preparative method of Me 2-(5-methyl-2-phenyl-4-oxazolyl)acetate and (S)-Me 2-(tert-butoxycarbonylamino)-3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]propanoate [or, i.e., N-[(1,1-dimethylethoxy)carbonyl]-O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]-L-tyrosine Me ester] were improved.
IT 185679-35-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of GW-409544 using O-[2-[methyl(phenyl)oxazolyl)ethyl]-L-tyrosine as reactant)
RN 185679-35-0 HCAPLUS
CN L-Tyrosine, O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]- (9CI) (CA INDEX NAME)

Updated Search

Absolute stereochemistry.



L4 ANSWER 3 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:1016040 HCAPLUS
DOCUMENT NUMBER: 141:424180
TITLE: Processes for making thiazolidinedione derivatives and compounds thereof
INVENTOR(S): Pospisilik, Karel; Zhu, Jie; Picha, Frantisek
PATENT ASSIGNEE(S): Synthon B.V., Neth.
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004101560	A1	20041125	WO 2004-EP5026	20040511
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005059708	A1	20050317	US 2004-842635	20040511
EP 1622898	A1	20060208	EP 2004-732115	20040511
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
CN 1812988	A	20060802	CN 2004-80018359	20040511
JP 2007502847	T	20070215	JP 2006-529780	20040511

PRIORITY APPLN. INFO.:	US 2003-469837P	P	20030513
	WO 2004-EP5026	W	20040511

OTHER SOURCE(S): MARPAT 141:424180
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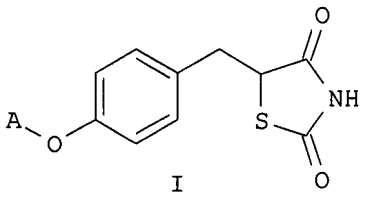

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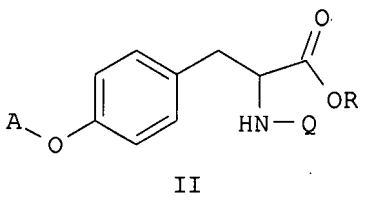


II

Updated Search

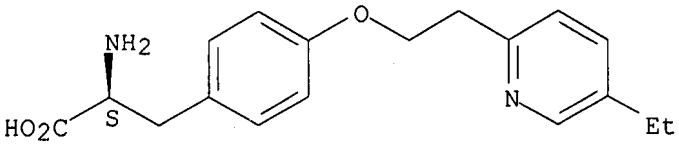
AB The invention relates processes for the synthesis of thiazolidinedione derivs. I (A is ethyl-2-pyridylethyl, [(2-pyridyl)methylamino]ethyl or [3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methyl] via reactions of amino acid intermediates II (same A, R is H or alkyl, Q is H or an amine-protecting group). The synthesis of pioglitazone is illustrated. Thus, 2-amino-3-[4-[2-(5-ethyl-2-pyridyl)ethoxy]phenyl]propionic acid, prepared by O-alkylation of L-tyrosine, underwent diazotization reaction to give the 2-bromo derivative which underwent cyclocondensation with thiourea to afford pioglitazone (isolated as the HCl salt).

IT 794591-56-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(Processes for making thiazolidinedione derivs. and compds. thereof)

RN 794591-56-3 HCAPLUS

CN L-Tyrosine, O-[2-(5-ethyl-2-pyridinyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:996131 HCAPLUS

DOCUMENT NUMBER: 141:424428

TITLE: Intermediate compound, namely O-[2-(5-ethylpyridin-2-yl)ethyl]tyrosine, which is used for the preparation of the antidiabetic agent pioglitazone, and methods for its preparation and conversion to pioglitazone

INVENTOR(S): Duran, Lopez Ernesto

PATENT ASSIGNEE(S): Medichem, S.A., Spain

SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Spanish

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004099147	A1	20041118	WO 2004-ES70031	20040504
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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
ES 2219180	A1	20041116	ES 2003-1075	20030509

Updated Search

ES 2219180	B1	20060301			
CA 2525190	A1	20041118	CA 2004-2525190		20040504
EP 1623977	A1	20060208	EP 2004-731028		20040504
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK					
US 2007083050	A1	20070412	US 2006-555659		20061219
PRIORITY APPLN. INFO.:			ES 2003-1075	A	20030509
			WO 2004-ES70031	W	20040504

OTHER SOURCE(S): CASREACT 141:424428; MARPAT 141:424428

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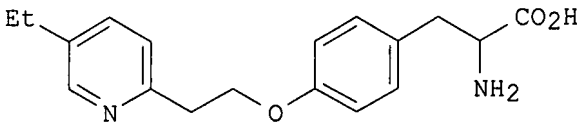

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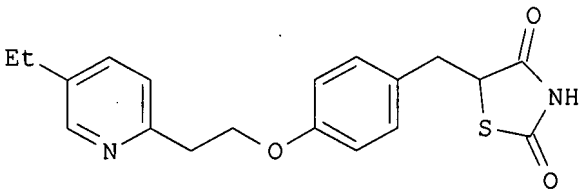

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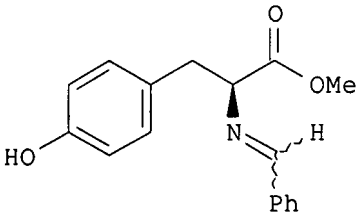

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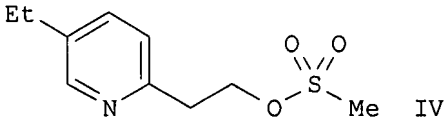


IV

AB The invention relates to the novel O-substituted tyrosine derivative I, including pure or mixed enantiomers, racemates, salts, solvates, and hydrates. I and its stereoisomers and compds. are new key intermediates for the preparation of the antidiabetic agent pioglitazone (II). The invention also relates to a method of obtaining I from a natural product, L-tyrosine, in which the amino group, in the form of an aromatic imine group, is protected by an aldehyde or ketone. The invention further relates to a method of obtaining II from the intermediate compound I. The critical feature of the invention is protection of the tyrosine N-terminal as an imine, which allows etherification of the phenolic tyrosine OH group to occur without competing N-alkylation. Complete racemization during the process allows the more desirable racemic I to be prepared from the more readily available L-tyrosine. For instance, L-tyrosine was treated with SOCl2 in refluxing MeOH to give the Me ester, which was treated with PhCHO at room temperature in CH2Cl2 to give doubly protected tyrosine III. This phenolic compound was etherified with the mesylate IV (preparation given) using K2CO3 and Bu4N+Br- in PhMe at 70°, and the protected product was deprotected in situ first with acid (2N HCl) and then with base (50% NaOH), both at

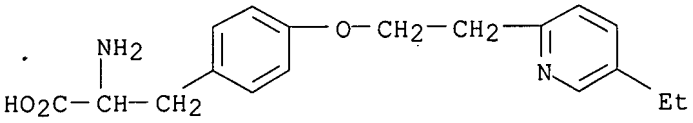
Updated Search

70°, to give racemic I in 62.8% overall yield from L-tyrosine. Diazotization of the amino group in I in the presence of HBr gave the corresponding bromo compound, which was cyclized with thiourea to give the 2-imine derivative of II. Acid hydrolysis of the imine in refluxing aqueous HCl gave II in 40.7% yield from I. Four comparative processes for preparing I, using other standard amine protecting groups instead of a benzaldehyde imine, were examined Overall yields of I from L-tyrosine were 24.1% for Boc, 20.7% for Cbz, 11.5% for Ac, and poor (unisolated) for EtOCO, vs. 62.8% for benzylidene.

IT 795316-22-2P, O-[2-(5-Ethylpyridin-2-yl)ethyl]-DL-tyrosine
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(target intermediate; intermediate compound which is used for the preparation of pioglitazone)

RN 795316-22-2 HCAPLUS

CN Tyrosine, O-[2-(5-ethyl-2-pyridinyl)ethyl]- (9CI) (CA INDEX NAME)

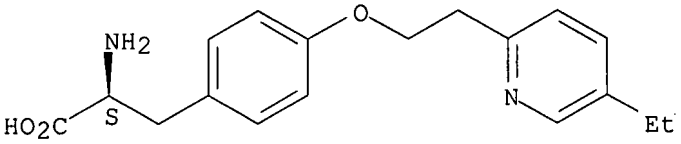


IT 794591-56-3P, O-[2-(5-Ethylpyridin-2-yl)ethyl]-L-tyrosine
795316-27-7P, O-[2-(5-Ethylpyridin-2-yl)ethyl]-D-tyrosine
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(target intermediate; intermediate compound which is used for the preparation of pioglitazone)

RN 794591-56-3 HCAPLUS

CN L-Tyrosine, O-[2-(5-ethyl-2-pyridinyl)ethyl]- (9CI) (CA INDEX NAME)

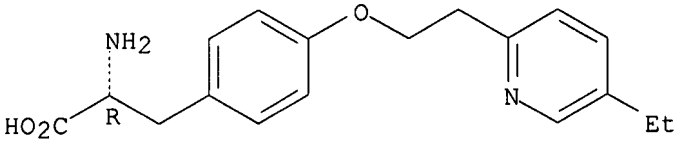
Absolute stereochemistry.



RN 795316-27-7 HCAPLUS

CN D-Tyrosine, O-[2-(5-ethyl-2-pyridinyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN

Updated Search

ACCESSION NUMBER: 2004:459234 HCAPLUS
DOCUMENT NUMBER: 141:153305
TITLE: Site-Specific Insertion of Spin-Labeled L-Amino Acids in Xenopus Oocytes
AUTHOR(S): Shafer, Aaron M.; Kalai, Tamas; Liu, Sarah Qiao Bin; Hideg, Kalman; Voss, John C.
CORPORATE SOURCE: Department of Biological Chemistry, University of California, Davis, CA, 95616, USA
SOURCE: Biochemistry (2004), 43(26), 8470-8482
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:153305

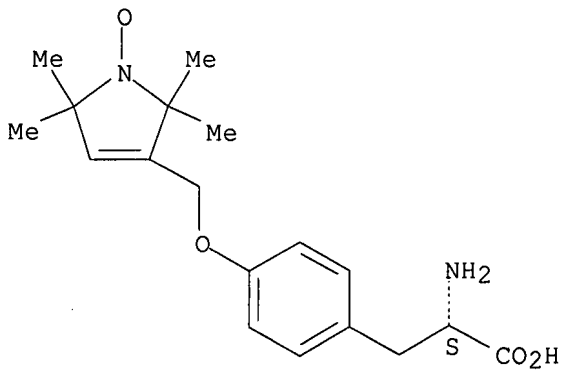
AB Site-specific insertion of modified amino acids in proteins expressed in living cells is an emerging field holding great promise for elucidating protein structure-function relationships, expression levels, localization, and activation states in a complex milieu. To evaluate the efficiency of amino acids modified to carry either a nitroxide spin probe or a fluorescence probe, we have developed a screen using the levels of functional luciferase protein expressed in Xenopus oocytes. Natural and modified amino acids were targeted to position 14 in firefly luciferase using an amber mutation or introducing the four-codon nucleotide GGGU. Using the amber stop codon, the incorporation efficiencies of injected tRNA charged with the native phenylalanine residue, a fluorescent NBD-alanine, or nitroxide-labeled cysteine and tyrosine amino acids ranged from 1% to 18%. While the NBD-amino acid derivative gave higher incorporation levels, the EPR signals from the spin-labeled amino acids allow for the direct assessment of aminoacylation extent and stability. Applying the four-base codon for the first time in Xenopus oocytes, we found the incorporation efficiencies were significantly lowered compared to results using the three-base amber codon. The studies presented here provide quant. assessment of protein expression levels when using nonsense suppression to site-specifically label proteins with spectroscopic probes in oocytes. Finally, the effect of a 77-base RNA aptamer known to inhibit the eucaryotic release factor of protein synthesis was tested for its influence on nonsense incorporation in Xenopus oocytes. The combination of A34 and charged suppressor tRNA produced a 3-fold increase in the expressed TAG14-luciferase level, compared to the use of charged suppressor tRNA alone.

IT 729580-43-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(site-specific insertion of spin-labeled L-amino acids in Xenopus oocytes)

RN 729580-43-2 HCAPLUS
CN 1H-Pyrrol-1-yloxy, 3-[[4-[(2S)-2-amino-2-carboxyethyl]phenoxy]methyl]-2,5-dihydro-2,2,5,5-tetramethyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Updated Search



REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

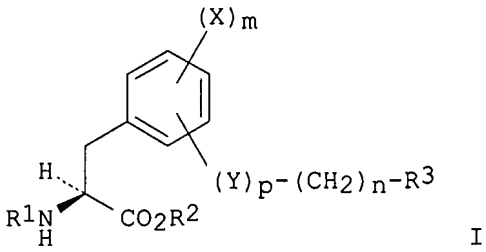
L4 ANSWER 6 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:633643 HCAPLUS
DOCUMENT NUMBER: 139:180343
TITLE: Preparation of aromatic amino acid derivatives as anticancer agents
INVENTOR(S): Endo, Hitoshi; Kanai, Yoshikatsu; Tsujihara, Kenji; Saito, Kunio
PATENT ASSIGNEE(S): Japan
SOURCE: PCT Int. Appl., 124 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003066574	A1	20030814	WO 2003-JP1081	20030203
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2475434	A1	20030814	CA 2003-2475434	20030203
AU 2003208105	A1	20030902	AU 2003-208105	20030203
EP 1481965	A1	20041201	EP 2003-703151	20030203
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 2005119256	A1	20050602	US 2003-503125	20030203
CN 1630632	A	20050622	CN 2003-803549	20030203

PRIORITY APPLN. INFO.: JP 2002-31216 A 20020207
WO 2003-JP1081 W 20030203

OTHER SOURCE(S): MARPAT 139:180343
GI

Updated Search



I

AB Aromatic amino acid derivs. represented by the following general formula (I) or pharmacol. acceptable salts thereof [wherein R1 represents hydrogen or an amino-protecting group; R2 represents hydrogen, alkylaralkyl or aryl; R3 represents (1) halogeno, (2) aroylamino, (3) Ph substituted by lower alkyl, Ph, phenoxy, etc., (4) naphthyl or tetrahydronaphthyl optionally substituted by hydroxy, lower alkoxy or di(lower alkyl)amino, (5) an N-, O- and/or S-containing unsatd. monocyclic heterocycle group substituted by lower alkyl, Ph, naphthyl or tetrahydroquinolyl, or (6) an N-, O- and/or S-containing fused heterocycle group, which may be unsatd. or partly saturated, optionally substituted by oxo, carboxy, amino, lower alkyl, etc.; X represents halogeno, alkyl or alkoxy; Y represents oxygen or nitrogen; p is 0 or 1; m is 0, 1 or 2; and n is an integer of from 0 to 5] are prepared These compds. inhibit a transporter (LAT1) of essential amino acids which are one of the main nutrients for cancer cells and induce depletion of the essential amino acids in the cancer cells, thereby inhibit the proliferation of the cancer cells. Thus, 0.2 mL pyridine was added to a suspension of N-trifluoroacetyl-3-hydroxy-L-phenylalanine Et ester 159, 2-naphthaleneboronic acid 186, mol. sieve 4A 204, and Cu(OAc)2 153 mg in 7 mL CH2Cl2, stirred at room temperature for 16 h in air to give, after workup and silica gel chromatog., 89% N-trifluoroacetyl-3-(2-naphthyloxy)-L-phenylalanine Et ester (II). 0.5 N aqueous NaOH was added to a solution of II (94 mg) in 2 mL THF at 5°, stirred at 5° for 69 h, acidified with 1 N aqueous HCl to pH 3-4, and filtered to give 78% 3-(2-naphthyloxy)-L-phenylalanine (III). In an assay for a LAT1 inhibitory activity, III and 3-[3-(6-dimethylaminopyridyl)phenoxy]-L-phenylalanine in vitro showed IC50 of 0.1 and 0.01 μg/mL, resp., for inhibiting the uptake of [14C]-L-tyrosine by human prostatic cancer T24 cells.

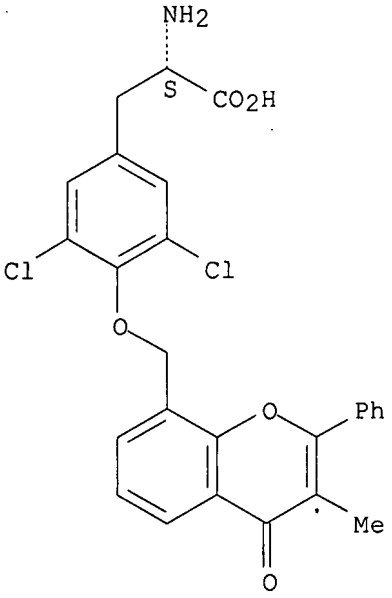
IT 579524-29-1P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of aromatic amino acid derivs. as anticancer agents for inhibiting proliferation of cancer cells by inhibiting essential amino acid transporter (LAT1))

RN 579524-29-1 HCAPLUS

CN L-Tyrosine, 3,5-dichloro-O-[(3-methyl-4-oxo-2-phenyl-4H-1-benzopyran-8-yl)methyl]- (9CI) (CA INDEX NAME)

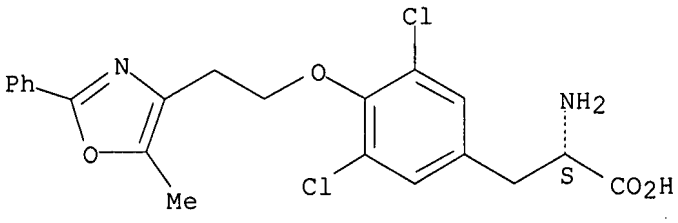
Absolute stereochemistry.

Updated Search



IT 579524-04-2P 579524-25-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of aromatic amino acid derivs. as anticancer agents for inhibiting
proliferation of cancer cells by inhibiting essential amino acid transporter (LAT1))
RN 579524-04-2 HCAPLUS
CN L-Tyrosine, 3,5-dichloro-O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]- (9CI) (CA INDEX NAME)

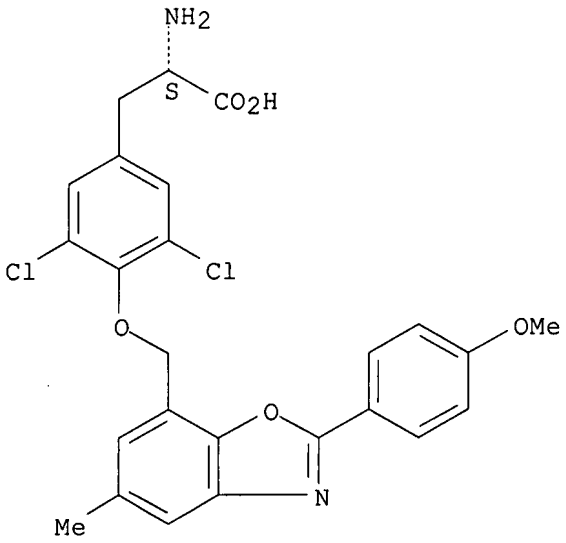
Absolute stereochemistry.



RN 579524-25-7 HCAPLUS
CN L-Tyrosine, 3,5-dichloro-O-[[2-(4-methoxyphenyl)-5-methyl-7-benzoxazolyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Updated Search



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:888693 HCAPLUS
DOCUMENT NUMBER: 137:385108
TITLE: Preparation of 2-amino-3-[3,5-dibromo-4-(3-bromobenzyloxy)phenyl]propionic acid and related compounds as thyroid hormone receptor antagonists for cardiac and metabolic disorders
INVENTOR(S): Malm, Johan; Brandt, Peter; Edvinsson, Karin; Ericsson, Thomas; Gordon, Sandra
PATENT ASSIGNEE(S): Karo Bio AB, Swed.
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002092550	A1	20021121	WO 2002-EP4193	20020415
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2446747	A1	20021121	CA 2002-2446747	20020415
AU 2002310850	A1	20021125	AU 2002-310850	20020415
EP 1387825	A1	20040211	EP 2002-735262	20020415
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
CN 1509267	A	20040630	CN 2002-809941	20020415
JP 2004533450	T	20041104	JP 2002-589436	20020415
US 2004220147	A1	20041104	US 2004-477676	20040610

Updated Search

PRIORITY APPLN. INFO.: GB 2001-11861 A 20010515
WO 2002-EP4193 W 20020415

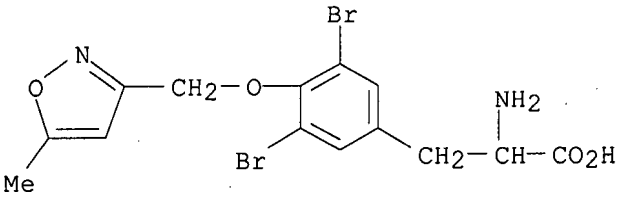
OTHER SOURCE(S): MARPAT 137:385108

AB Compds. 3,5,4-R2,R3(R1CH2O)C6H2(CH2)nCHR4R5 [I; R1 = (un)substituted (hetero)aryl or cycloalkyl; R2, R3 = Cl, Br, (cyclo)alkyl, alkenyl, alkynyl; R4 = halo, OH, SH, NH2, alkylamino; R5 = CO2H, PO3H2, P(O)(OH)NH2, SO3H, COCO2H, CONHOH; n = 1 or 2], including all possible stereoisomers, prodrug esters, and radioactive forms, were prepared as thyroid receptor ligands, preferably antagonists, for the treatment of cardiac arrhythmias, thyrotoxicosis, subclin. hyperthyroidism, and liver diseases. Thus, the title acid was prepared from Boc-Tyr-OMe (Boc = tert-butoxycarbonyl) by bromination, etherification with 3-bromobenzyl bromide, and deprotection using TFA. I exhibited binding affinities to the thyroid hormone receptor α (ThRa) in the range of 100 nM to 10,000 nM. Compds. I exhibited binding affinities to the ThRa receptor in the range of 10 nM to 10,000 nM.

IT 475999-32-7P 475999-41-8P
RL: DGN (Diagnostic use); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of amino[(benzyloxy)phenyl]propionic acid derivs. and related compds. as thyroid hormone receptor antagonists for cardiac and metabolic disorders)

RN 475999-32-7 HCAPLUS

CN Tyrosine, 3,5-dibromo-O-[(5-methyl-3-isoxazolyl)methyl]- (9CI) (CA INDEX NAME)

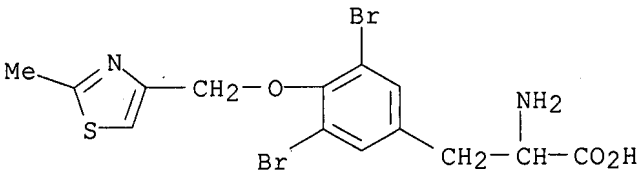


RN 475999-41-8 HCAPLUS

CN Tyrosine, 3,5-dibromo-O-[(2-methyl-4-thiazolyl)methyl]-, compd. with N,N-diethylethanamine (1:1) (9CI) (CA INDEX NAME)

CM 1

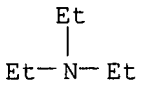
CRN 475999-40-7
CMF C14 H14 Br2 N2 O3 S



CM 2

CRN 121-44-8
CMF C6 H15 N

Updated Search

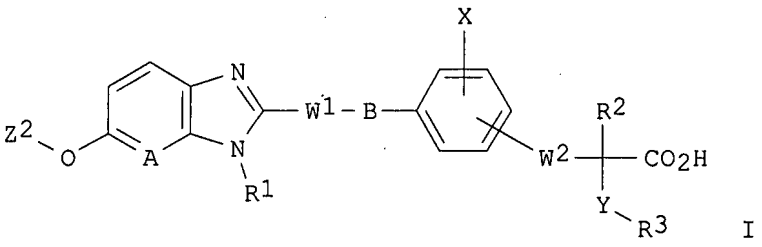


REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:516372 HCAPLUS
DOCUMENT NUMBER: 137:78955
TITLE: Preparation of benzimidazole-α-substituted carboxylic acid derivatives for prevention and/or treatment of diseases such as diabetes
INVENTOR(S): Fujita, Takashi; Wada, Kunio; Oguchi, Minoru; Honma, Hidehito; Fujiwara, Toshihiko; Iwabuchi, Haruo
PATENT ASSIGNEE(S): Sankyo Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 93 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2002193948	A	20020710	JP 2001-308762	20011004
PRIORITY APPLN. INFO.:			JP 2000-307158 A	20001006

OTHER SOURCE(S): MARPAT 137:78955
GI



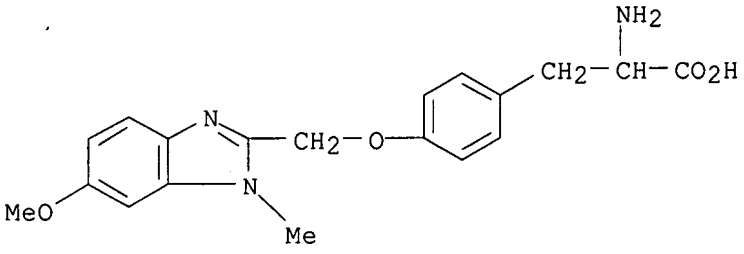
AB Disclosed are insulin-resistance improving agents, blood sugar-lowering agents, immune regulating agents, aldose reductase-inhibitors, 5-lipoxygenase-inhibitors, lipid peroxide formation-suppressing agents, peroxisome proliferator-activated receptor (PPAR)-activating agents leukotriene antagonists, fat cell-formation promoters, and calcium antagonists containing the title compds. [I; R1, R2, R3 = H, C1-6 alkyl, (un)substituted C6-10 aryl, (un)substituted C7-16 , C1-6 alkylsulfonyl, C1-6 haloalkylsulfonyl, (un)substituted C6-10 arylsulfonyl, C7-16 aralkylsulfonyl; A = N, CH; B = O, S; W1 = C1-6 alkylene; W2 = single bond, C1-8 alkylene; X = H, C1-6 alkyl, C1-6 haloalkyl, C1-6 alkoxy, halo, HO, cyano, NO2, C3-10 cycloalkyl, (un)substituted C6-10 aryl, (un)substituted C7-16 aralkyl, C1-7 aliphatic acyl, C4-11 cycloalkylcarbonyl, (un)substituted C7-11 arylcarbonyl, C8-17 aralkylcarbonyl, (un)substituted monocyclic heterocyclylcarbonyl, CONH2, (un)substituted C7-11 arylaminocarbonyl, (un)substituted NH2; Y = O, S(O)p (p = 0-2); Z2 = (un)substituted saturated heterocyclyl or C6-10 aryl] or pharmacol. acceptable

Updated Search

salts as the active ingredients. They are useful for the prevention and/or treatment of diabetes, impaired glucose tolerance, neurosis, cataract, coronary artery disease, and gestational diabetes. Thus, a solution of 3-[4-[[[[4-[4-(adamantan-1-yl)phenoxy]-2-(N-tert-butoxycarbonyl-N-methylamino)phenyl]amino]carbonyl]methoxy]phenyl]-2-(4-fluorobenzyloxy)propionic acid Me ester in 4 N HCl/dioxane was stirred at room temperature for 1 h to give 3-[4-[6-[4-(adamantan-1-yl)phenoxy]-1-methyl-1H-benzimidazol-2-ylmethoxy]phenyl]-2-(4-fluorobenzyloxy)propanoic acid Me ester which was stirred with a mixture of 2 n aqueous NaOH and methanol at room temperature for 2 h, treated with THF, stirred for 4 h, poured into water, and neutralized with HCl and aqueous NaHCO3 to give 3-[4-[[6-[4-(adamantan-1-yl)phenoxy]-1-methyl-1H-benzimidazol-2-yl]methoxy]phenyl]-2-(4-fluorobenzyloxy)propanoic acid (II). When a feed containing 0.01% II was fed to diabetic KK mice for 3 days, blood sugar level was lowered by 58.5%. A capsule, a tablet, and a granule formulation containing II were prepared

IT 440355-09-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzimidazole-α-substituted carboxylic acid derivs. for prevention and/or treatment of diseases such as diabetes and impaired glucose tolerance)

RN 440355-09-9 HCAPLUS
CN Tyrosine, O-[(6-methoxy-1-methyl-1H-benzimidazol-2-yl)methyl]-, dihydrochloride (9CI) (CA INDEX NAME)



●2 HCl

L4 ANSWER 9 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:629484 HCAPLUS
DOCUMENT NUMBER: 136:6304
TITLE: The synthesis of GW710936X to support the development of potent PPARγ agonists
AUTHOR(S): Reynolds, D. J.; Hermitage, S. A.
CORPORATE SOURCE: Chemical Development Division, Medicines Research Centre, GlaxoSmithKline Research and Development, Hertfordshire, SG1 2NY, UK
SOURCE: Tetrahedron (2001), 57(36), 7765-7770
CODEN: TETRAB; ISSN: 0040-4020
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 136:6304

AB (2S)-[(2-benzoyl-4-hydroxyphenyl)amino]-3-[4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl]propanoic acid (GW710936X) has been synthesized from

Updated Search

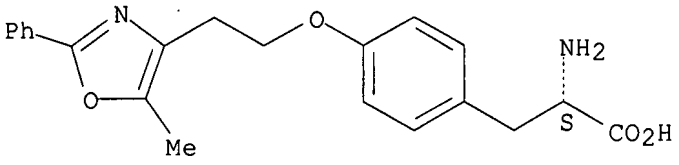
N-Cbz-L-tyrosine Me ester utilizing a copper(I)-catalyzed N-arylation as the key coupling step. The synthetic route was designed to be convergent and to facilitate ease of isolation of the unstable product that had proven to be unobtainable by concentration of exts. from biol. assays.

IT 185679-35-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of GW710936X to support the development of potent PPARγ agonists)

RN 185679-35-0 HCAPLUS

CN L-Tyrosine, O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:581856 HCAPLUS

DOCUMENT NUMBER: 135:152795

TITLE: Process for synthesis of oxazolethoxyphenylpropanoic acid derivative for use as NIDDM medicament

INVENTOR(S): Davis, Roman; Kennedy, Andrew

PATENT ASSIGNEE(S): Glaxo Group Limited, UK

SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001057001	A1	20010809	WO 2001-EP1041	20010201

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2000-2667 A 20000204

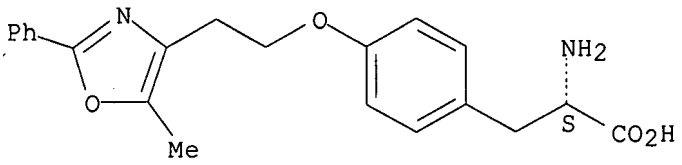
AB Process for synthesis of calcium salt of (2S)-2-{[(Z)-1-methyl-3-oxo-3-phenyl-1-propenyl]amino}-3-{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]phenyl}propanoic acid and physiol. acceptable solvates thereof, useful as NIDDM medicament is disclosed.

IT 353239-35-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of oxazolethoxyphenylpropanoic acid derivative for NIDDM

Updated Search

medicament)
RN 353239-35-7 HCAPLUS
CN L-Tyrosine, O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]-, monohydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

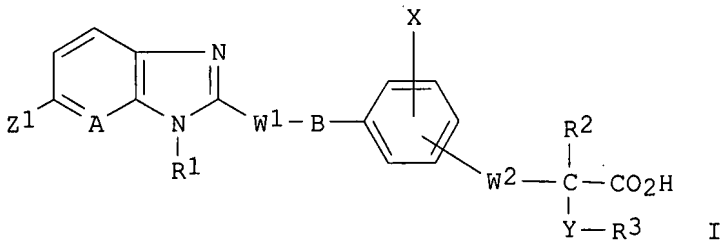
L4 ANSWER 11 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:725618 HCAPLUS
DOCUMENT NUMBER: 133:281783
TITLE: Preparation of benzimidazolylalkoxyphenylalkanoic acid derivatives for the treatment of diabetes and other diseases
INVENTOR(S): Fujita, Takashi; Wada, Kunio; Oguchi, Minoru; Honma, Hidehito; Fujiwara, Toshihiko; Iwabuchi, Haruo
PATENT ASSIGNEE(S): Sankyo Company, Ltd., Japan
SOURCE: PCT Int. Appl., 235 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000059889	A1	20001012	WO 2000-JP2215	20000406
W: AU, BR, CA, CN, CZ, HU, ID, IL, IN, KR, MX, NO, NZ, PL, RU, TR, US, ZA				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2369871	A1	20001012	CA 2000-2369871	20000406
JP 2001097955	A	20010410	JP 2000-104701	20000406
EP 1167357	A1	20020102	EP 2000-915361	20000406
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
TR 200102908	T2	20020422	TR 2001-2908	20000406
BR 2000009593	A	20020618	BR 2000-9593	20000406
HU 200200895	A2	20021128	HU 2002-895	20000406
AU 760163	B2	20030508	AU 2000-36707	20000406
NZ 514661	A	20030630	NZ 2000-514661	20000406
RU 2219172	C2	20031220	RU 2001-127083	20000406
IN 2001KN01023	A	20050311	IN 2001-KN1023	20011001
ZA 2001008168	A	20030218	ZA 2001-8168	20011004
NO 2001004849	A	20011127	NO 2001-4849	20011005
MX 2001PA10109	A	20020604	MX 2001-PA10109	20011005
US 2003069294	A1	20030410	US 2001-972206	20011005

Updated Search

US 6596751	B2	20030722			
US 2004002512	A1	20040101	US 2003-376942		20030228
PRIORITY APPLN. INFO.:			JP 1999-99286	A	19990406
			JP 1999-215141	A	19990729
			WO 2000-JP2215	W	20000406
			US 2001-972206	A3	20011005

OTHER SOURCE(S): MARPAT 133:281783
GI



I

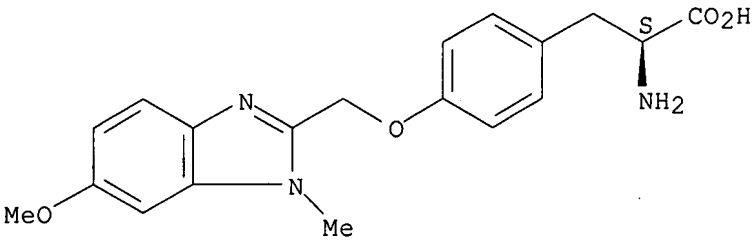
AB The title compds. I [R1 is alkyl or the like; R2 is hydrogen or the like; R3 is hydrogen or the like; A is CH or the like; B is oxygen or the like; W1 is C1-C8 alkylene; W2 is a single bond or C1-C8 alkylene; X is hydrogen or the like; Y is oxygen or the like; and Z1 is alkoxy or the like] are prepared Feed containing 0.01% 3-[4-[6-(3,5-di-tert-butyl-4-hydroxyphenylthio)-1-methyl-1H-benzimidazol-2-ylmethoxy]phenyl]-2-(4-fluorobenzyloxy)propionic acid decreased blood sugar in diabetic mice by 40.8%. Formulations are given.

IT 299175-43-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of benzimidazolylalkoxyphenylalkanoic acid derivs. for treatment of diabetes and other diseases)

RN 299175-43-2 HCAPLUS

CN L-Tyrosine, O-[(6-methoxy-1-methyl-1H-benzimidazol-2-yl)methyl]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.



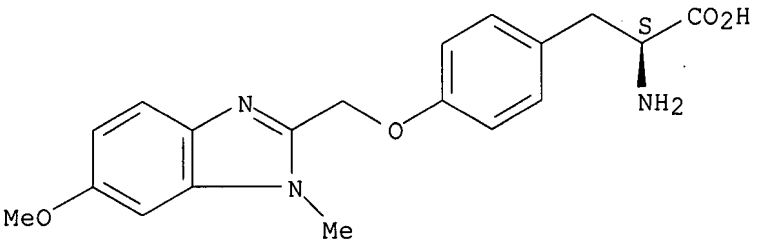
●2 HCl

IT 299176-09-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of benzimidazolylalkoxyphenylalkanoic acid derivs. for

Updated Search

treatment of diabetes and other diseases)
RN 299176-09-3 HCAPLUS
CN L-Tyrosine, O-[(6-methoxy-1-methyl-1H-benzimidazol-2-yl)methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

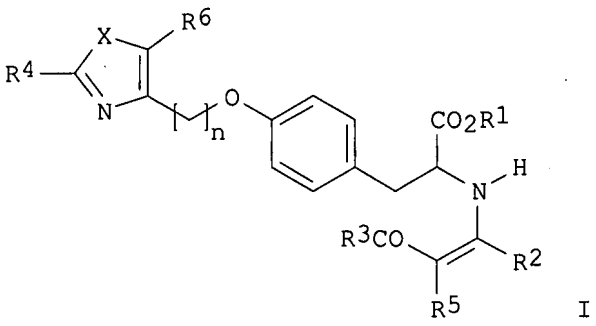
L4 ANSWER 12 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:117035 HCAPLUS
DOCUMENT NUMBER: 132:151814
TITLE: Preparation of substituted oxazoles and thiazoles as hPPAR gamma and hPPAR alpha activators
INVENTOR(S): Collins, Jon Loren; Dezube, Milana; Oplinger, Jeffrey Alan; Willson, Timothy Mark
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 110 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000008002	A1	20000217	WO 1999-EP5666	19990805
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2339773	A1	20000217	CA 1999-2339773	19990805
AU 9957310	A	20000228	AU 1999-57310	19990805
EP 1102757	A1	20010530	EP 1999-944335	19990805
EP 1102757	B1	20040414		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
TR 200100372	T2	20010921	TR 2001-200100372	19990805
BR 9912866	A	20011030	BR 1999-12866	19990805
HU 200103469	A2	20020128	HU 2001-3469	19990805
EE 200100074	A	20020617	EE 2001-74	19990805
AT 264313	T	20040415	AT 1999-944335	19990805
ES 2220110	T3	20041201	ES 1999-944335	19990805
ZA 2001000983	A	20020305	ZA 2001-983	20010205
NO 2001000628	A	20010406	NO 2001-628	20010206

Updated Search

MX 2001PA01419	A	20010930	MX 2001-PA1419		20010207
HR 2001000095	A1	20020228	HR 2001-95		20010207
US 6498174	B1	20021224	US 2001-762445		20010222
IN 2001KN00166	A	20050311	IN 2001-KN166		20010313
PRIORITY APPLN. INFO.:			GB 1998-17118	A	19980807
			WO 1999-EP5666	W	19990805

OTHER SOURCE(S): MARPAT 132:151814
GI



I

AB The title compds. [I; R1 = H, alkyl; R2 = H, alkyl, haloalkyl; R3 = alkyl, cycloalkyl, cycloalkenyl, etc.; R4 = (un)substituted 5-6 membered heterocyclyl containing at least one O, N or S atom, Ph; R5 = H, halo, alkyl, haloalkyl; R6 = H, alkyl; X = O, S; n = 1-3], which are dual activators of hPPARγ and hPPARα, were prepared Thus, refluxing a suspension of (2S)-2-amino-3-{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]phenyl}propanoic acid (preparation given) and benzoylacetone in MeOH and trimethylorthoformate afforded 43% (2S)-(Z)-I [R1 = H; R2 = Me; R3 = Ph; R4 = Ph; R5 = H; R6 = Me; X = O; n = 2] which showed 39% glucose reduction in rats.

IT 258347-27-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of substituted oxazoles and thiazoles as hPPAR gamma and hPPAR alpha activators)

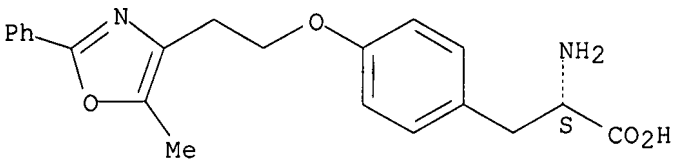
RN 258347-27-2 HCAPLUS

CN L-Tyrosine, O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]-, 2,2,2-trifluoroacetate (1:1) (CA INDEX NAME)

CM 1

CRN 185679-35-0
CMF C21 H22 N2 O4

Absolute stereochemistry.

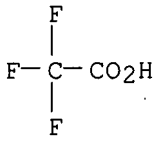


CM 2

CRN 76-05-1

Updated Search

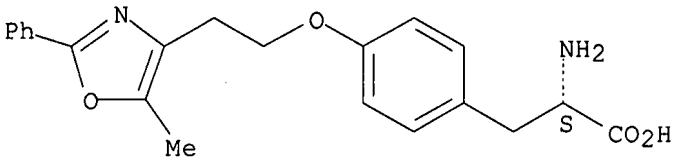
CMF C2 H F3 O2



IT 185679-35-0P 258346-81-5P 258346-84-8P
258346-85-9P 258346-86-0P 258346-87-1P
258346-88-2P 258346-89-3P 258346-91-7P
258346-92-8P 258346-94-0P 258346-96-2P
258346-98-4P 258347-07-8P 258347-09-0P
258347-11-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of substituted oxazoles and thiazoles as hPPAR gamma and hPPAR alpha activators)

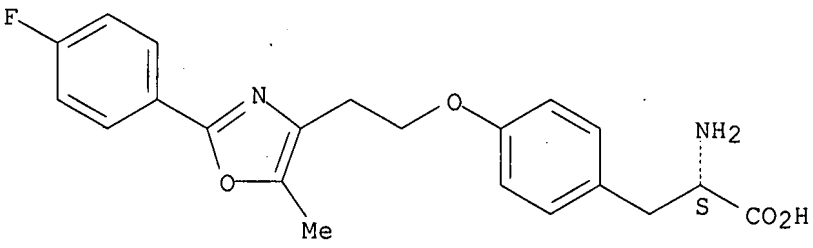
RN 185679-35-0 HCAPLUS
CN L-Tyrosine, O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 258346-81-5 HCAPLUS
CN L-Tyrosine, O-[2-[2-(4-fluorophenyl)-5-methyl-4-oxazolyl]ethyl]- (9CI) (CA INDEX NAME)

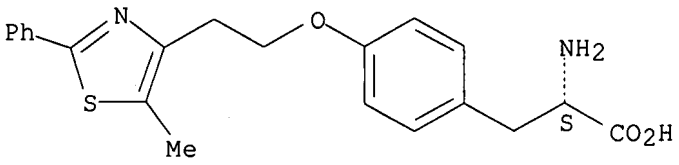
Absolute stereochemistry.



RN 258346-84-8 HCAPLUS
CN L-Tyrosine, O-[2-(5-methyl-2-phenyl-4-thiazolyl)ethyl]- (9CI) (CA INDEX NAME)

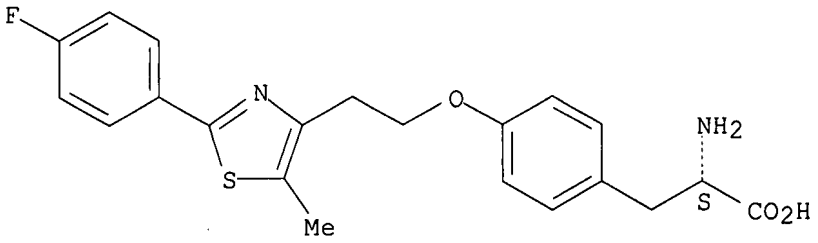
Absolute stereochemistry.

Updated Search



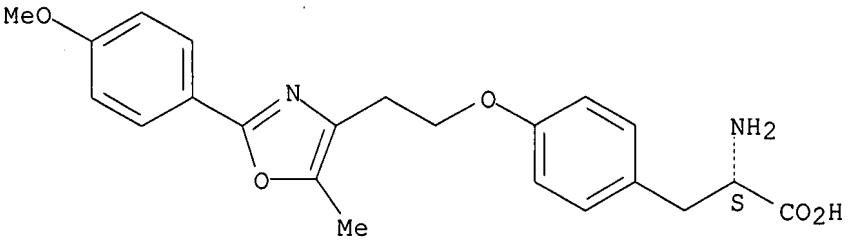
RN 258346-85-9 HCAPLUS
CN L-Tyrosine, O-[2-[2-(4-fluorophenyl)-5-methyl-4-thiazolyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



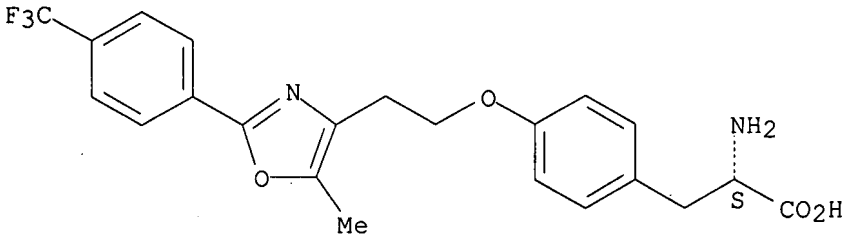
RN 258346-86-0 HCAPLUS
CN L-Tyrosine, O-[2-[2-(4-methoxyphenyl)-5-methyl-4-oxazolyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 258346-87-1 HCAPLUS
CN L-Tyrosine, O-[2-[5-methyl-2-[4-(trifluoromethyl)phenyl]-4-oxazolyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

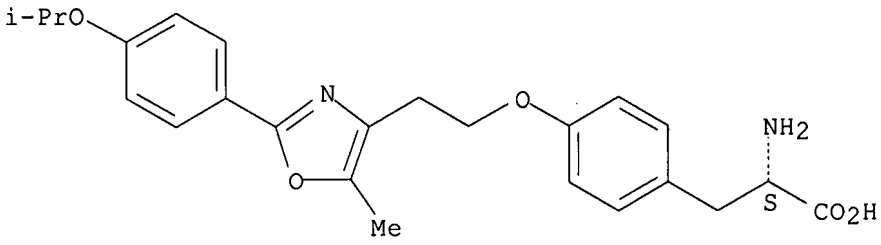


RN 258346-88-2 HCAPLUS
CN L-Tyrosine, O-[2-[5-methyl-2-[4-(1-methylethoxy)phenyl]-4-oxazolyl]ethyl]-

Updated Search

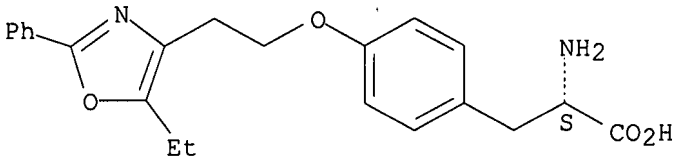
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



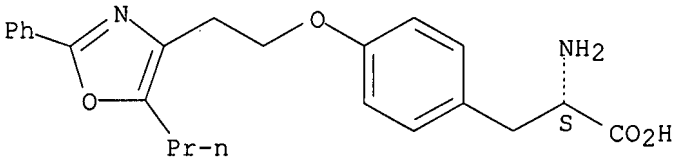
RN 258346-89-3 HCAPLUS
CN L-Tyrosine, O-[2-(5-ethyl-2-phenyl-4-oxazolyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



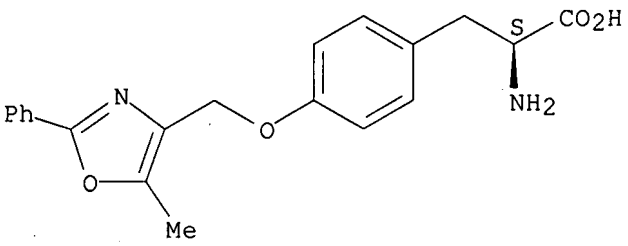
RN 258346-91-7 HCAPLUS
CN L-Tyrosine, O-[2-(2-phenyl-5-propyl-4-oxazolyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 258346-92-8 HCAPLUS
CN L-Tyrosine, O-[(5-methyl-2-phenyl-4-oxazolyl)methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

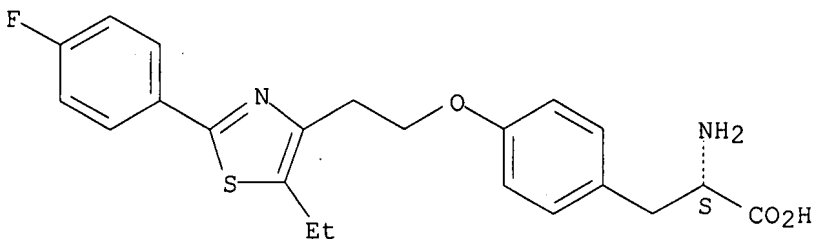


RN 258346-94-0 HCAPLUS

Updated Search

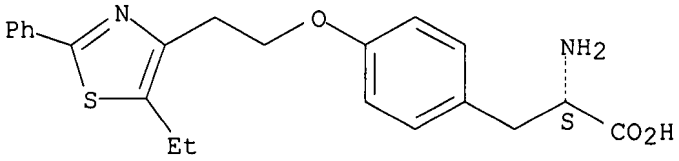
CN L-Tyrosine, O-[2-[5-ethyl-2-(4-fluorophenyl)-4-thiazolyl]ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



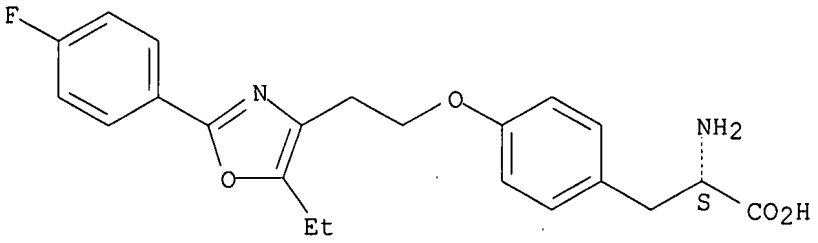
RN 258346-96-2 HCAPLUS
CN L-Tyrosine, O-[2-(5-ethyl-2-phenyl-4-thiazolyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 258346-98-4 HCAPLUS
CN L-Tyrosine, O-[2-[5-ethyl-2-(4-fluorophenyl)-4-oxazolyl]ethyl]- (9CI) (CA INDEX NAME)

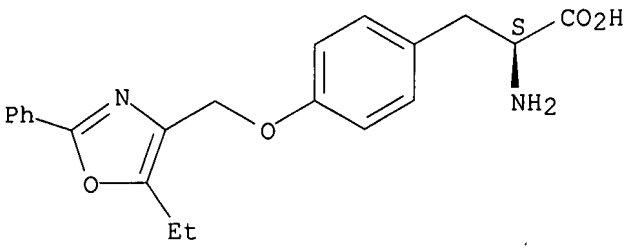
Absolute stereochemistry.



RN 258347-07-8 HCAPLUS
CN L-Tyrosine, O-[(5-ethyl-2-phenyl-4-oxazolyl)methyl]- (9CI) (CA INDEX NAME)

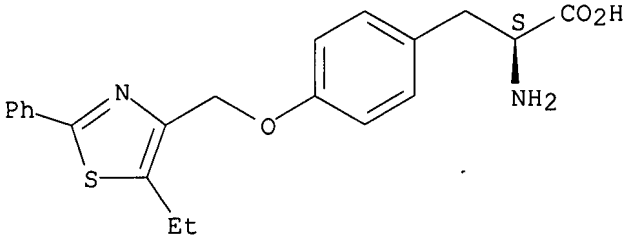
Absolute stereochemistry.

Updated Search



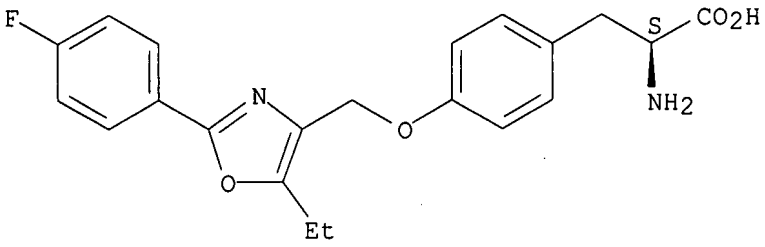
RN 258347-09-0 HCAPLUS
CN L-Tyrosine, O-[(5-ethyl-2-phenyl-4-thiazolyl)methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 258347-11-4 HCAPLUS
CN L-Tyrosine, O-[[5-ethyl-2-(4-fluorophenyl)-4-oxazolyl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:77060 HCAPLUS
DOCUMENT NUMBER: 126:89361
TITLE: Preparation of (oxazolyl)alkoxyphenylpropionic acid derivatives as hypoglycemics and hypolipemics
INVENTOR(S): Takeno, Hidekazu; Ikemoto, Tomoyuki; Saitoh, Isao; Watanabe, Kazuhiro
PATENT ASSIGNEE(S): Sumitomo Metal Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1

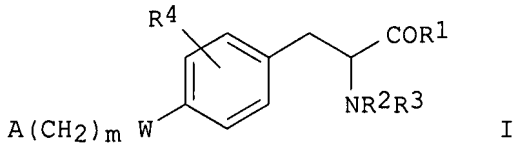
Updated Search

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9638415	A1	19961205	WO 1996-JP1380	19960524
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML				
JP 08325263	A	19961210	JP 1995-133460	19950531
AU 9657791	A	19961218	AU 1996-57791	19960524
PRIORITY APPLN. INFO.:			JP 1995-133460 A	19950531
			WO 1996-JP1380 W	19960524

OTHER SOURCE(S): MARPAT 126:89361

GI



I

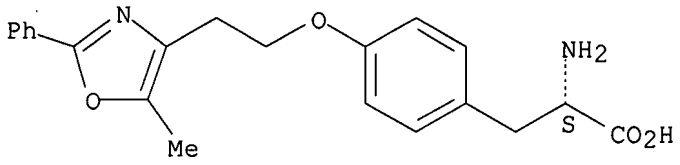
AB The title compds. I [A represents a nitrogenous heterocycle; W represents oxygen or carbonyl; R1 represents hydroxy, an ester residue or a substituted imide group; and R2 and R3 represent each hydrogen, alkyl, aralkyl, alkanoyl, benzoyl, etc.; R4 = H, nitro, etc.; m = 0 - 2] are prepared The title compds. at 10 mg/kg gave 32 to 54% decrease of blood glucose in diabetic mice.

IT 185679-35-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of (oxazolyl)alkoxyphenylpropionic acid derivs. as hypoglycemics and hypolipemics)

RN 185679-35-0 HCAPLUS

CN L-Tyrosine, O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 14 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1983:13648 HCAPLUS

DOCUMENT NUMBER: 98:13648

TITLE: Chemical and biochemical properties of p-cresol methylhydroxylase

AUTHOR(S): McIntire, William S.; Hopper, D. J.; Edmondson, D. E.; Singer, Thomas P.

Updated Search

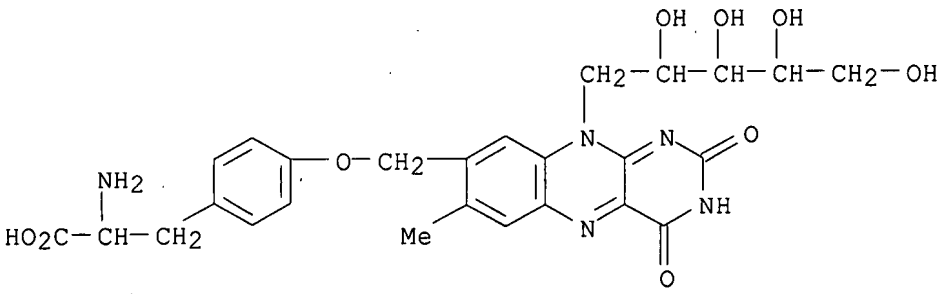
CORPORATE SOURCE: Mol. Biol. Div., VA Med. Cent., San Francisco, CA, USA
SOURCE: Developments in Biochemistry (1982), 21(Flavins Flavoproteins), 483-7
CODEN: DEBIDR; ISSN: 0165-1714
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Flavin peptides (generated by peptic digestion) were isolated from p-cresol methylhydroxylases (I) from several Pseudomonas putida strains and characterized. Peptide sequencing revealed N-dansyl-tyrosine as the N-terminal amino acid derivative Apparently, the phenolic O of the tyrosine residue is blocked by the flavin. The flavin was associated with tyrosine with a molar ratio of 1:1. The putative 8α-tyrosylflavin peptide was synthesized in its riboflavin form and judged identical with the isolated aminoacyl riboflavin (the flavin occurs naturally as FAD in I). Reduction of the 8α-O-tyrosylflavin by Na2S2O4, followed by reoxidn. resulted in the release of tyrosine. In I, tyrosine was not released by reduction-oxidation, indicating the stabilization of the tyrosine-flavin linkage in the holoenzyme. Titration with p-cresol gave virtually the same results. As the substrate donates electrons (e-) in pairs but I accepts 3 e-, interenzymic e- transfer might be implicated.

IT 38065-74-6
RL: BIOL (Biological study)
(as cresol methylhydroxylase aminoacyl-flavin model)

RN 38065-74-6 HCAPLUS

CN Riboflavin, α8-[4-(2-amino-2-carboxyethyl)phenoxy]-, (S)- (9CI) (CA INDEX NAME)



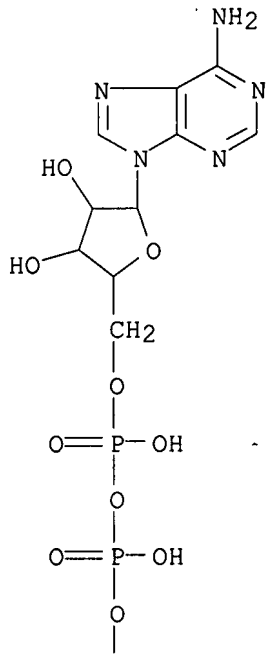
IT 74850-08-1
RL: BIOL (Biological study)
(in cresol methylhydroxylase of Pseudomonas putida)

RN 74850-08-1 HCAPLUS

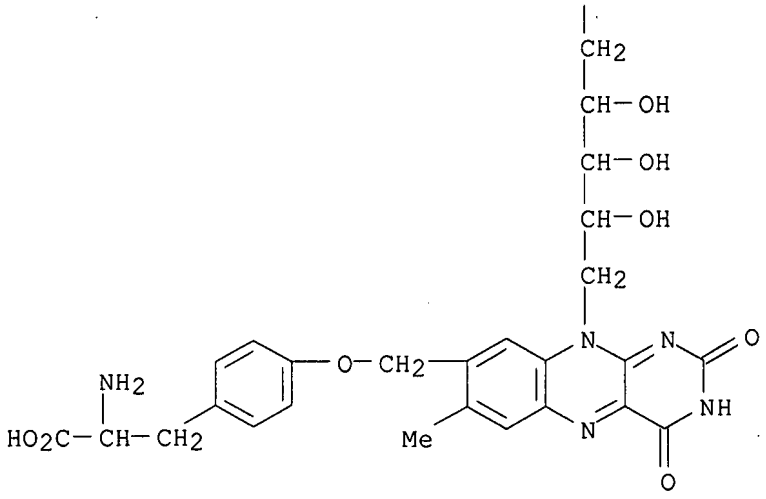
CN Riboflavin 5'-(trihydrogen diphosphate), α8-[4-(2-amino-2-carboxyethyl)phenoxy]-, P'→5'-ester with adenosine, (S)- (9CI) (CA INDEX NAME)

Updated Search

PAGE 1-A



PAGE 2-A

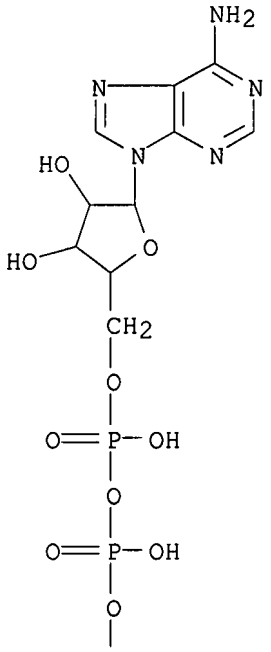


L4 ANSWER 15 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1981:420324 HCAPLUS
DOCUMENT NUMBER: 95:20324
TITLE: 8α-(O-Tyrosyl)flavin adenine dinucleotide, the prosthetic group of bacterial p-cresol methylhydroxylase
AUTHOR(S): McIntire, William; Edmondson, Dale E.; Hopper, David J.; Singer, Thomas P.
CORPORATE SOURCE: Mol. Biol. Div., VA Med. Cent., San Francisco, CA,

Updated Search

94121, USA
SOURCE: Biochemistry (1981), 20(11), 3068-75
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 8α(O-Tyrosyl)riboflavin (I) has been synthesized by condensation of the Cu(II) complex of L-tyrosine with 8α-bromotetraacetylriboflavin. The structure of I was proven by absorption and 1H NMR spectroscopy and by chemical degradation, which yielded 1 mol tyrosine/mol flavin. I comigrated with the (aminoacyl)riboflavin isolated from the p-cresol methylhydroxylase (II) of Pseudomonas putida, and both showed identical absorption and fluorescence spectral properties. I as well as the flavin-containing decapeptide from II undergoes reductive cleavage to form riboflavin and FAD, resp., on anaerobic treatment with dithionite. In contrast, native II, on reduction with dithionite, yields a reduced flavin via a red (anionic) flavosemiquinone intermediate, which remains covalently bound to the protein even under denaturing conditions. I bound to apoflavodoxin is also not cleaved on reduction with dithionite, but, instead, a blue (neutral) semiquinone of I is generated, which is resistant to further reduction with dithionite. Three II activities, isolated from different strains of Pseudomonas putida, differing in mol. weight and Km values for substrates, contain the same peptide at the flavin site. These data provide definitive proof for the existence of I in nature.
IT 74850-08-1
RL: BIOL (Biological study)
(as p-cresol methylhydroxylase prosthetic group)
RN 74850-08-1 HCAPLUS
CN Riboflavin 5'-(trihydrogen diphosphate), α8-[4-(2-amino-2-carboxyethyl)phenoxy]-, P'→5'-ester with adenosine, (S)- (9CI) (CA INDEX NAME)

PAGE 1-A



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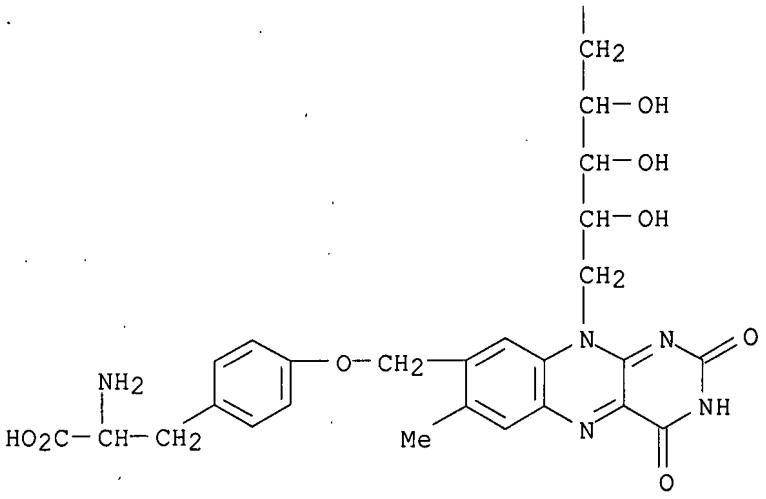
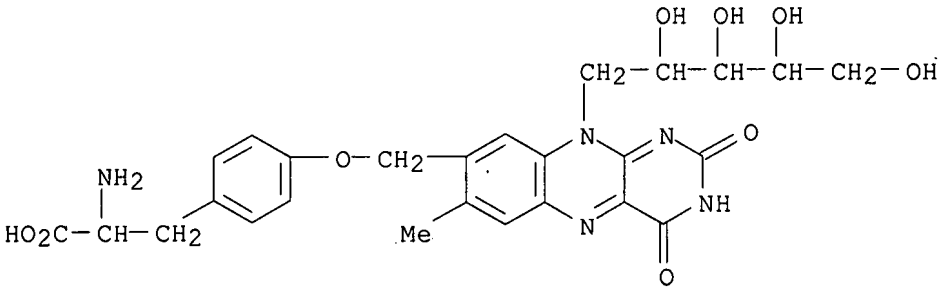


IT 38065-74-6P
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(preparation and properties of)
RN 38065-74-6 HCAPLUS
CN Riboflavin, α8-[4-(2-amino-2-carboxyethyl)phenoxy]-, (S)- (9CI) (CA INDEX NAME)



L4 ANSWER 16 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1980:527842 HCAPLUS
DOCUMENT NUMBER: 93:127842
TITLE: 8α-O-tyrosyl-FAD: a new form of covalently bound flavin from p-cresol methylhydroxylase
AUTHOR(S): McIntire, William; Edmondson, Dale E.; Singer, Thomas P.; Hopper, David J.
CORPORATE SOURCE: Mol. Biol. Div., VA Med. Cent., San Francisco, CA, 94121, USA
SOURCE: Journal of Biological Chemistry (1980), 255(14), 6553-5
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB p-Cresol methylhydroxylase from Pseudomonas putida contains covalently bound flavin and a type c cytochrome. A flavin undecapeptide was isolated from peptic digests of the protein which shows the typical 3-banded

Updated Search

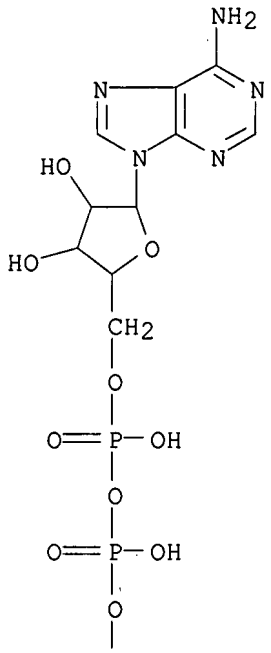
spectrum of flavins with the 2nd absorption peak shifted hypsochromically to 360 nm, indicating substitution at position 8α. Aminopeptidase digestion gave an aminoacyl flavin, with a further shift of the 2nd band to 352 nm at neutral pH. The dinucleotide nature of the flavin was indicated by a major change in mobility in TLC on treatment of the peptide with nucleotide pyrophosphatase and a further change on subsequent dephosphorylation with alkaline phosphatase. The fluorescence of the peptide is trivial, but oxidation with performic acid at 0 and 40° for 1 h increased it to .apprx.10 and 35% of that of riboflavin, resp. Despite this indication that the compound may be a flavin thioether, no cysteine was detected in the peptide. The performic acid-oxidized flavin peptide showed no pH dependence of the fluorescence in the range pH 3.2-7, and, in accord with this, no histidine was present in hydrolyzates. The flavin was identified as 8α-O-tyrosylriboflavin on the basis of the following evidence: dansylation of the flavin and acid hydrolysis yielded N-dansyltyrosine, instead of the expected O-dansyl or N,O-didansyltyrosine. Brief hydrolysis of the flavin peptide with aminopeptidase M gave an aminoacyl flavin which contained riboflavin and tyrosine in equal amts. 8α-O-Tyrosyl-FAD is the N-terminal residue of the peptide. Noncovalent interaction between the flavin and this tyrosine, as well as a tryptophan residue, seems responsible for the virtually complete quenching of the fluorescence.

IT 74850-08-1
RL: BIOL (Biological study)
(as cresol 4-methylhydroxylase prosthetic group)

RN 74850-08-1 HCAPLUS

CN Riboflavin 5'-(trihydrogen diphosphate), α8-[4-(2-amino-2-carboxyethyl)phenoxy]-, P'→5'-ester with adenosine, (S)- (9CI) (CA INDEX NAME)

PAGE 1-A



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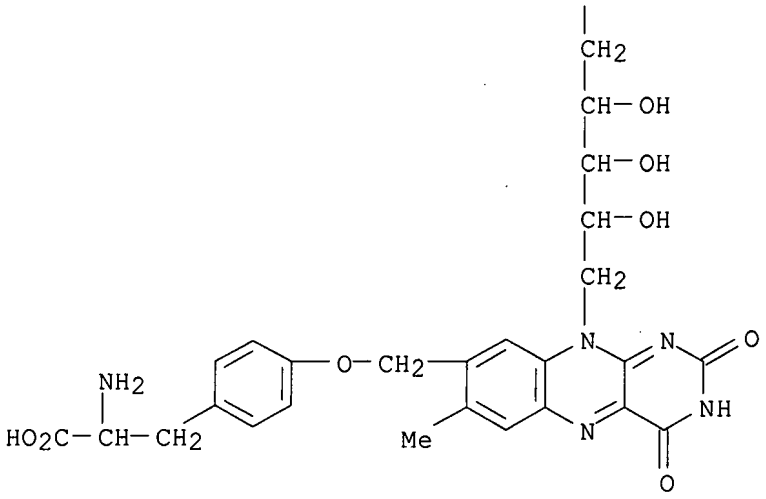
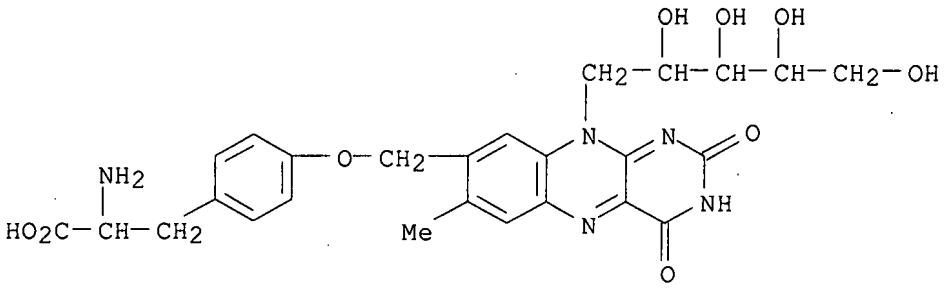
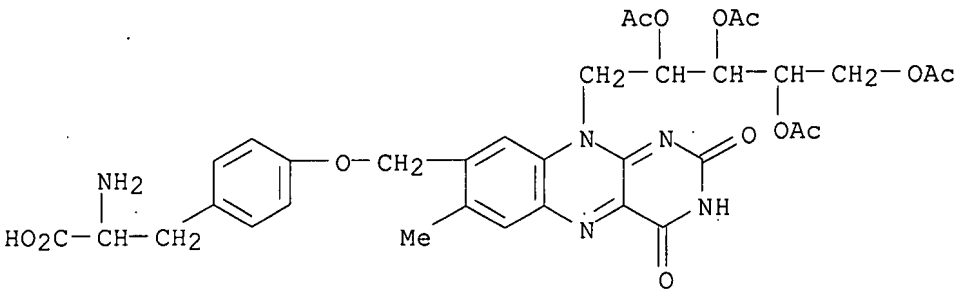


L4 ANSWER 17 OF 17 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1972:448772 HCAPLUS
DOCUMENT NUMBER: 77:48772
TITLE: Synthesis and properties of 8α-substituted riboflavines of biological importance
AUTHOR(S): Kenney, William C.; Walker, Wolfram H.
CORPORATE SOURCE: Mol. Biol. Div., Veterans Adm. Hosp., San Francisco, CA, USA
SOURCE: FEBS Letters (1972), 20(3), 297-301
CODEN: FEBLAL; ISSN: 0014-5793
DOCUMENT TYPE: Journal
LANGUAGE: English
GI For diagram(s), see printed CA Issue.
AB 8α-Substituted riboflavines (I,II, III, and IV) were prepared Thus, 8α-bromotetraacetylriboflavine (V) was reacted with α-(N-benzoyl)-L-lysine amide acetate in DMF to give a product which on hydrolysis gave 8α-(Nε-lysyl)riboflavine (I). Similarly prepared were 8α-(O-tyrosyl)riboflavine (II) and 8α-sulforiboflavine (III). The carboxylic acid (IV) was obtained from V by performic acid oxidation Properties of I, II, III, and IV are compared with those of some other 8α-substituted riboflavines.
IT 38065-74-6P 38065-77-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 38065-74-6 HCAPLUS
CN Riboflavin, α8-[4-(2-amino-2-carboxyethyl)phenoxy]-, (S)- (9CI) (CA INDEX NAME)



Updated Search

RN 38065-77-9 HCAPLUS
CN Riboflavin, α8-[4-(2-amino-2-carboxyethyl)phenoxy]-,
2',3',4',5'-tetraacetate, (S)- (9CI) (CA INDEX NAME)



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FILE COVERS 1907-1966
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

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This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

=> d his

(FILE 'HOME' ENTERED AT 21:58:30 ON 24 SEP 2007)

FILE 'REGISTRY' ENTERED AT 21:58:36 ON 24 SEP 2007
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L2 2 S L1
L3 35 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 22:03:28 ON 24 SEP 2007
L4 17 S L3
L5 0 S L4 AND CHUPAK, L?/AU

Updated Search

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L6             0 S L4 AND BOYER, F?/AU
L7             0 S L4 AND HAGEN, S?/AU
L8             0 S L4 AND KANEKO, T?/AU
L9             0 S L4 AND LALL, M?/AU
L10           32 S 4 AND PETTERSSON, M?/AU
L11            0 S L4 AND LALL, M?/AU
L12            0 S L4 AND PETTERSSON, M?/AU
L13            0 S L4 AND PRASAD, J?/AU

     FILE 'CAOLD' ENTERED AT 22:11:39 ON 24 SEP 2007

=> s l3
L14           0 L3

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CA SUBSCRIBER PRICE                                       0.00     -13.26

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DICTIONARY FILE UPDATES:  23 SEP 2007  HIGHEST RN 947726-74-1

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TSCA INFORMATION NOW CURRENT THROUGH June 29, 2007

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  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

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Uploading C:\Documents and Settings\brobinson1\My
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L15     STRUCTURE UPLOADED

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INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.11


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CA SUBSCRIBER PRICE                                   0.00     -13.26

FILE 'HCAPLUS' ENTERED AT 22:18:23 ON 24 SEP 2007
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FILE COVERS 1907 - 24 Sep 2007  VOL 147 ISS 14
FILE LAST UPDATED: 23 Sep 2007  (20070923/ED)

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 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

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Updated Search
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L9            0 S L4 AND LALL, M?/AU
L10          32 S 4 AND PETTERSSON, M?/AU
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L15             STRUCTURE UPLOADED
L16          50 S L15
L17       42185 S L16 FULL

     FILE 'HCAPLUS' ENTERED AT 22:18:23 ON 24 SEP 2007
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=> s l18 and l4
L19          10 L18 AND L4

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CA SUBSCRIBER PRICE                             0.00     -13.26

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STRUCTURE FILE UPDATES:   23 SEP 2007  HIGHEST RN 947726-74-1
DICTIONARY FILE UPDATES:  23 SEP 2007  HIGHEST RN 947726-74-1

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  Please note that search-term pricing does apply when
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REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of


Updated Search
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experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

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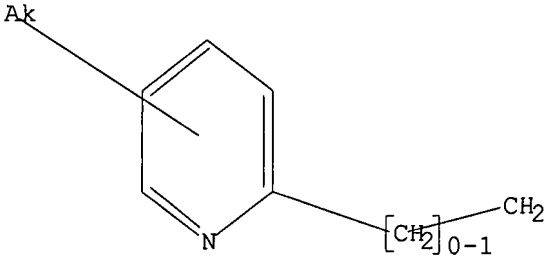

Structure attributes must be viewed using STN Express query preparation.

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SEARCH TIME: 00.00.01

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L21 50 SEA SSS SAM L20

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Updated Search

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CA SUBSCRIBER PRICE                                    0.00     -13.26

FILE 'HCAPLUS' ENTERED AT 22:21:33 ON 24 SEP 2007
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FILE COVERS 1907 - 24 Sep 2007  VOL 147 ISS 14
FILE LAST UPDATED: 23 Sep 2007  (20070923/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

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L23       6111 L22/RCT
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L2            2 S L1
L3           35 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 22:03:28 ON 24 SEP 2007
L4           17 S L3
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L7            0 S L4 AND HAGEN, S?/AU
L8            0 S L4 AND KANEKO, T?/AU
L9            0 S L4 AND LALL, M?/AU
L10          32 S 4 AND PETTERSSON, M?/AU
L11           0 S L4 AND LALL, M?/AU
L12           0 S L4 AND PETTERSSON, M?/AU
L13           0 S L4 AND PRASAD, J?/AU

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L14           0 S L3

     FILE 'REGISTRY' ENTERED AT 22:11:45 ON 24 SEP 2007
L15             STRUCTURE UPLOADED
L16          50 S L15
L17       42185 S L16 FULL


Updated Search
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L19           10 S L18 AND L4

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L21           50 S L20
L22        46885 S L20 FULL

     FILE 'HCAPLUS' ENTERED AT 22:21:33 ON 24 SEP 2007
L23         6111 S L22/RCT

=> s l23 and l19
L24           3 L23 AND L19

=> d l24, ibib abs hitstr, 1-3

L24  ANSWER 1 OF 3  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2004:1016040  HCAPLUS
DOCUMENT NUMBER:          141:424180
TITLE:                    Processes for making thiazolidinedione derivatives and
                          compounds thereof
INVENTOR(S):              Pospisilik, Karel; Zhu, Jie; Picha, Frantisek
PATENT ASSIGNEE(S):       Synthon B.V., Neth.
SOURCE:                   PCT Int. Appl., 47 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
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             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
             SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
             SN, TD, TG
     US 2005059708         A1    20050317    US 2004-842635          20040511
     EP 1622898            A1    20060208    EP 2004-732115          20040511
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     CN 1812988            A     20060802    CN 2004-80018359        20040511
     JP 2007502847         T     20070215    JP 2006-529780          20040511
PRIORITY APPLN. INFO.:                       US 2003-469837P      P  20030513
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OTHER SOURCE(S):          MARPAT 141:424180
GI
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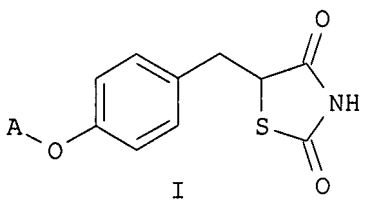
Updated Search



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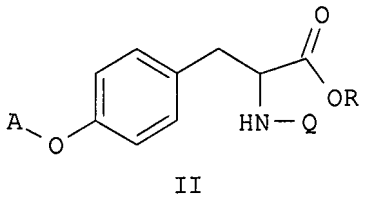


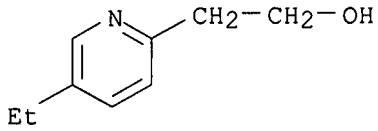
II

AB The invention relates processes for the synthesis of thiazolidinedione derivs. I (A is ethyl-2-pyridylethyl, [(2-pyridyl)methylamino]ethyl or [3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methyl] via reactions of amino acid intermediates II (same A, R is H or alkyl, Q is H or an amine-protecting group). The synthesis of pioglitazone is illustrated. Thus, 2-amino-3-[4-[2-(5-ethyl-2-pyridyl)ethoxy]phenyl]propionic acid, prepared by O-alkylation of L-tyrosine, underwent diazotization reaction to give the 2-bromo derivative which underwent cyclocondensation with thiourea to afford pioglitazone (isolated as the HCl salt).

IT 5223-06-3 144809-27-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(Processes for making thiazolidinedione derivs. and compds. thereof)

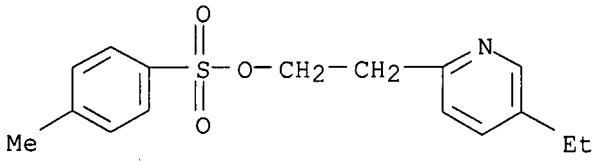
RN 5223-06-3 HCAPLUS

CN 2-Pyridineethanol, 5-ethyl- (CA INDEX NAME)



RN 144809-27-8 HCAPLUS

CN 2-Pyridineethanol, 5-ethyl-, 4-methylbenzenesulfonate (ester) (9CI) (CA INDEX NAME)



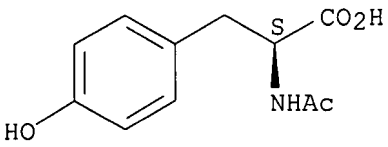
IT 537-55-3P, n Acetyl L-Tyrosine 840-97-1P, n Acetyl L-Tyrosine ethyl ester 105355-26-8P 124731-84-6P 144809-26-7P 674798-32-4P 794591-56-3P 794591-57-4P 794591-58-5P 794591-59-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(Processes for making thiazolidinedione derivs. and compds. thereof)

RN 537-55-3 HCAPLUS

CN L-Tyrosine, N-acetyl- (CA INDEX NAME)

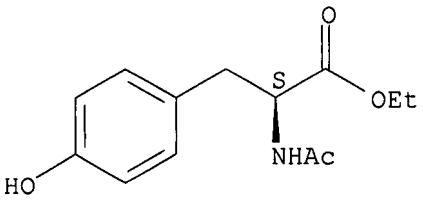
Absolute stereochemistry. Rotation (+).

Updated Search

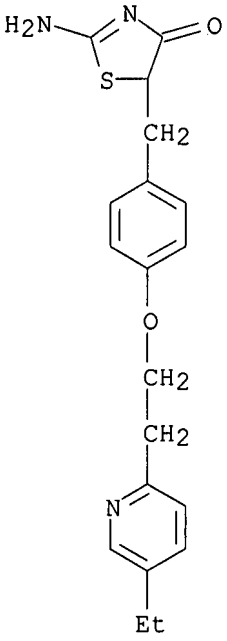


RN 840-97-1 HCAPLUS
CN L-Tyrosine, N-acetyl-, ethyl ester (CA INDEX NAME)

Absolute stereochemistry.



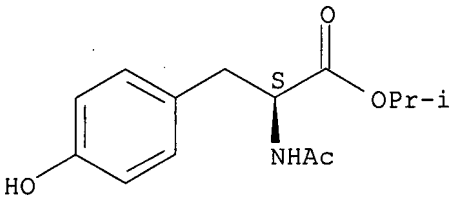
RN 105355-26-8 HCAPLUS
CN 4(5H)-Thiazolone, 2-amino-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]- (CA INDEX NAME)



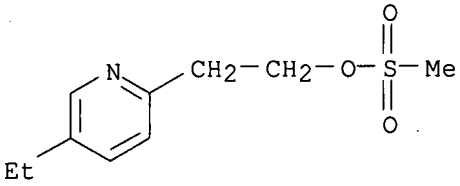
RN 124731-84-6 HCAPLUS
CN L-Tyrosine, N-acetyl-, 1-methylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

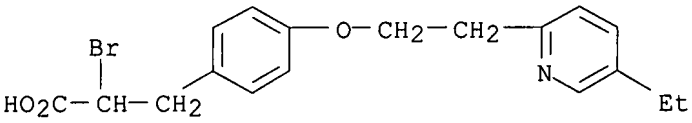
Updated Search



RN 144809-26-7 HCAPLUS
CN 2-Pyridineethanol, 5-ethyl-, methanesulfonate (ester) (9CI) (CA INDEX NAME)

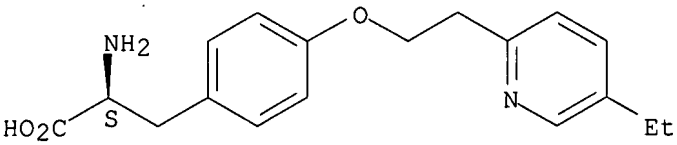


RN 674798-32-4 HCAPLUS
CN Benzenepropanoic acid, α-bromo-4-[2-(5-ethyl-2-pyridinyl)ethoxy]- (9CI) (CA INDEX NAME)



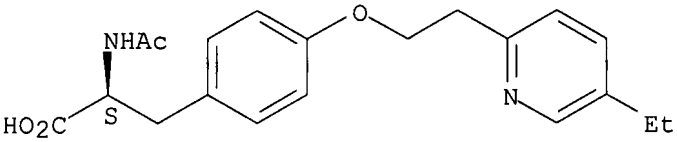
RN 794591-56-3 HCAPLUS
CN L-Tyrosine, O-[2-(5-ethyl-2-pyridinyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 794591-57-4 HCAPLUS
CN L-Tyrosine, N-acetyl-O-[2-(5-ethyl-2-pyridinyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

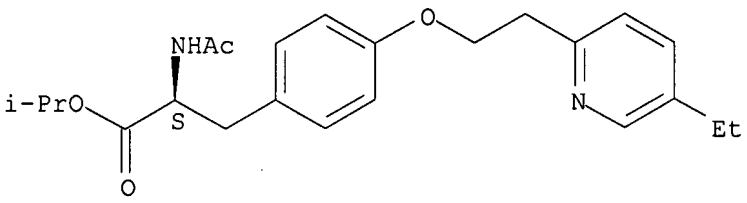


RN 794591-58-5 HCAPLUS
CN L-Tyrosine, N-acetyl-O-[2-(5-ethyl-2-pyridinyl)ethyl]-, 1-methylethyl

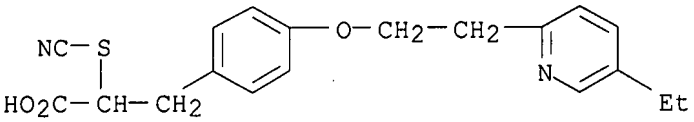
Updated Search

ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 794591-59-6 HCAPLUS
CN Benzenepropanoic acid, 4-[2-(5-ethyl-2-pyridinyl)ethoxy]-α-thiocyanato- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:996131 HCAPLUS
DOCUMENT NUMBER: 141:424428
TITLE: Intermediate compound, namely O-[2-(5-ethylpyridin-2-yl)ethyl]tyrosine, which is used for the preparation of the antidiabetic agent pioglitazone, and methods for its preparation and conversion to pioglitazone
INVENTOR(S): Duran, Lopez Ernesto
PATENT ASSIGNEE(S): Medichem, S.A., Spain
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Spanish
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004099147	A1	20041118	WO 2004-ES70031	20040504
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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ES 2219180	B1	20060301		
CA 2525190	A1	20041118	CA 2004-2525190	20040504
EP 1623977	A1	20060208	EP 2004-731028	20040504

Updated Search

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK

US 2007083050 A1 20070412 US 2006-555659 20061219
PRIORITY APPLN. INFO.: ES 2003-1075 A 20030509
WO 2004-ES70031 W 20040504
OTHER SOURCE(S): CASREACT 141:424428; MARPAT 141:424428

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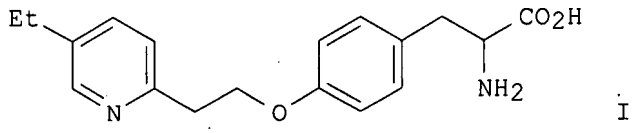

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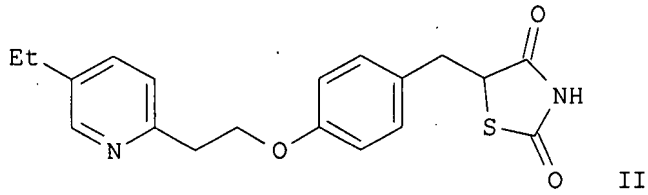

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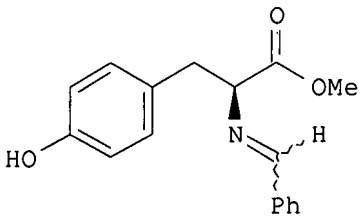

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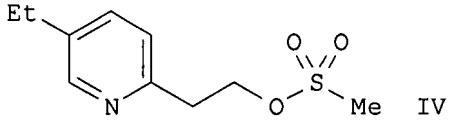


IV

AB The invention relates to the novel O-substituted tyrosine derivative I, including pure or mixed enantiomers, racemates, salts, solvates, and hydrates. I and its stereoisomers and compds. are new key intermediates for the preparation of the antidiabetic agent pioglitazone (II). The invention also relates to a method of obtaining I from a natural product, L-tyrosine, in which the amino group, in the form of an aromatic imine group, is protected by an aldehyde or ketone. The invention further relates to a method of obtaining II from the intermediate compound I. The critical feature of the invention is protection of the tyrosine N-terminal as an imine, which allows etherification of the phenolic tyrosine OH group to occur without competing N-alkylation. Complete racemization during the process allows the more desirable racemic I to be prepared from the more readily available L-tyrosine. For instance, L-tyrosine was treated with SOCl2 in refluxing MeOH to give the Me ester, which was treated with PhCHO at room temperature in CH2Cl2 to give doubly protected tyrosine III. This phenolic compound was etherified with the mesylate IV (preparation given) using K2CO3 and Bu4N+Br- in PhMe at 70°, and the protected product was deprotected in situ first with acid (2N HCl) and then with base (50% NaOH), both at 70°, to give racemic I in 62.8% overall yield from L-tyrosine. Diazotization of the amino group in I in the presence of HBr gave the corresponding bromo compound, which was cyclized with thiourea to give the

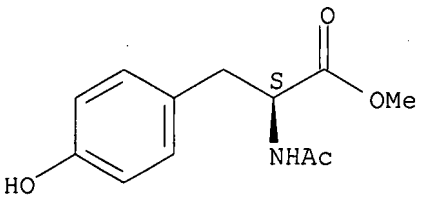
Updated Search

2-imine derivative of II. Acid hydrolysis of the imine in refluxing aqueous HCl gave II in 40.7% yield from I. Four comparative processes for preparing I, using other standard amine protecting groups instead of a benzaldehyde imine, were examined Overall yields of I from L-tyrosine were 24.1% for Boc, 20.7% for Cbz, 11.5% for Ac, and poor (unisolated) for EtOCO, vs. 62.8% for benzylidene.

IT 2440-79-1P, N-Acetyl-L-tyrosine methyl ester 4326-36-7P, N-Boc-L-tyrosine methyl ester 13512-31-7P, N-Cbz-L-tyrosine methyl ester 215596-38-6P, N-(Ethoxycarbonyl)-L-tyrosine methyl ester 795316-23-3P, N-Boc-O-[2-(5-ethylpyridin-2-yl)ethyl]-L-tyrosine methyl ester 795316-24-4P, N-Boc-O-[2-(5-ethylpyridin-2-yl)ethyl]-L-tyrosine 795316-25-5P, O-[2-(5-Ethylpyridin-2-yl)ethyl]-L-tyrosine methyl ester 795316-26-6P, N-Cbz-O-[2-(5-ethylpyridin-2-yl)ethyl]-L-tyrosine methyl ester
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(comparison process intermediate; intermediate compound which is used for the preparation of pioglitazone)

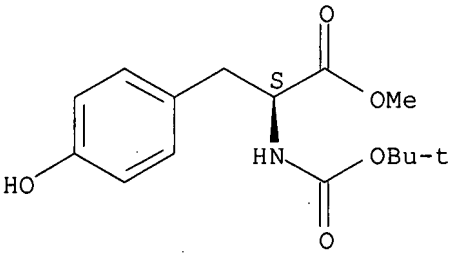
RN 2440-79-1 HCAPLUS
CN L-Tyrosine, N-acetyl-, methyl ester (CA INDEX NAME)

Absolute stereochemistry.



RN 4326-36-7 HCAPLUS
CN L-Tyrosine, N-[(1,1-dimethylethoxy)carbonyl]-, methyl ester (CA INDEX NAME)

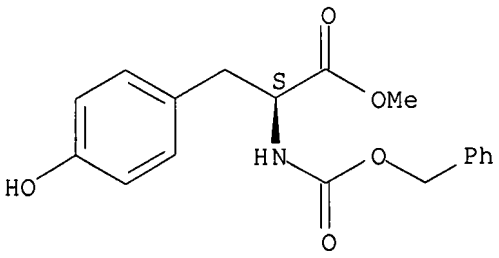
Absolute stereochemistry. Rotation (+).



RN 13512-31-7 HCAPLUS
CN L-Tyrosine, N-[(phenylmethoxy)carbonyl]-, methyl ester (CA INDEX NAME)

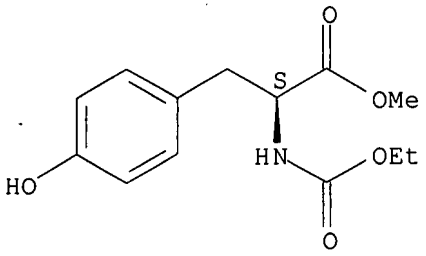
Absolute stereochemistry. Rotation (-).

Updated Search



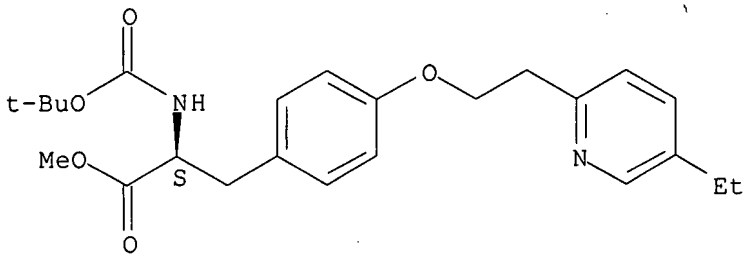
RN 215596-38-6 HCAPLUS
CN L-Tyrosine, N-(ethoxycarbonyl)-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



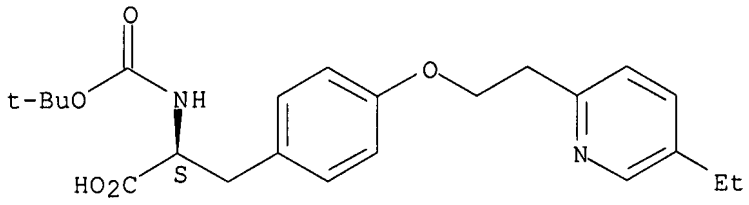
RN 795316-23-3 HCAPLUS
CN L-Tyrosine, N-[(1,1-dimethylethoxy)carbonyl]-O-[2-(5-ethyl-2-pyridinyl)ethyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 795316-24-4 HCAPLUS
CN L-Tyrosine, N-[(1,1-dimethylethoxy)carbonyl]-O-[2-(5-ethyl-2-pyridinyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

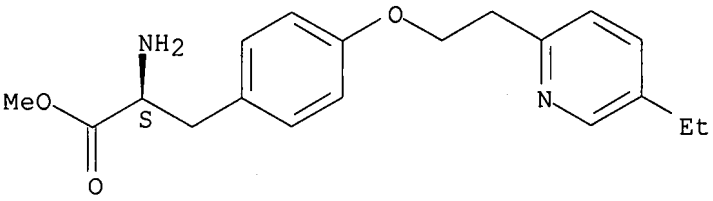


RN 795316-25-5 HCAPLUS
CN L-Tyrosine, O-[2-(5-ethyl-2-pyridinyl)ethyl]-, methyl ester (9CI) (CA

Updated Search

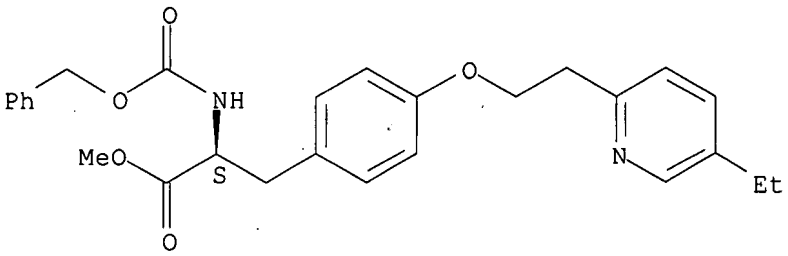
INDEX NAME)

Absolute stereochemistry.



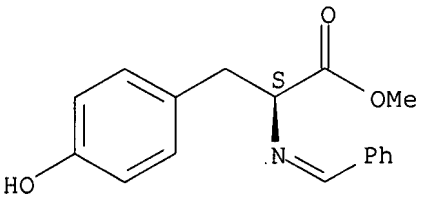
RN 795316-26-6 HCAPLUS
CN L-Tyrosine, O-[2-(5-ethyl-2-pyridinyl)ethyl]-N-[(phenylmethoxy)carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



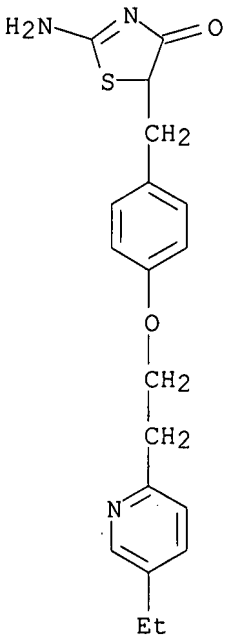
IT 69955-04-0P, N-Benzylidene-L-tyrosine methyl ester
105355-26-8P, Pioglitazone 2-imine 144809-26-7P,
2-(5-Ethylpyridin-2-yl)ethyl methanesulfonate 674798-32-4P,
α-Bromo-4-[2-(5-ethylpyridin-2-yl)ethoxy]benzenepropanoic acid
795316-28-8P, N-Benzylidene-O-[2-(5-ethylpyridin-2-yl)ethyl]-L-tyrosine methyl ester
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process intermediate; intermediate compound which is used for the preparation
of pioglitazone)
RN 69955-04-0 HCAPLUS
CN L-Tyrosine, N-(phenylmethylene)-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

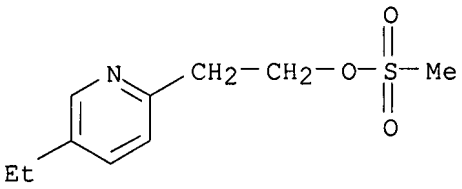


RN 105355-26-8 HCAPLUS
CN 4(5H)-Thiazolone, 2-amino-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]- (CA INDEX NAME)

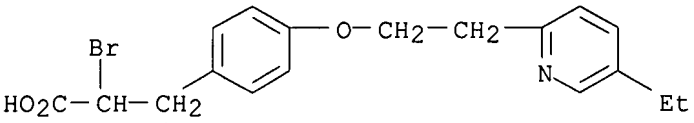
Updated Search



RN 144809-26-7 HCAPLUS
CN 2-Pyridineethanol, 5-ethyl-, methanesulfonate (ester) (9CI) (CA INDEX NAME)



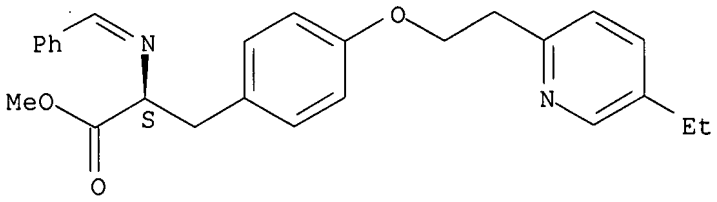
RN 674798-32-4 HCAPLUS
CN Benzenepropanoic acid, α-bromo-4-[2-(5-ethyl-2-pyridinyl)ethoxy]- (9CI) (CA INDEX NAME)



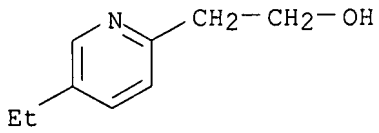
RN 795316-28-8 HCAPLUS
CN L-Tyrosine, O-[2-(5-ethyl-2-pyridinyl)ethyl]-N-(phenylmethylene)-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

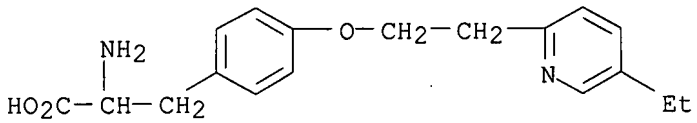
Updated Search



IT 5223-06-3, 2-(5-Ethylpyridin-2-yl)ethanol
RL: RCT (Reactant); RACT (Reactant or reagent)
(starting material; intermediate compound which is used for the preparation of
pioglitazone)
RN 5223-06-3 HCAPLUS
CN 2-Pyridineethanol, 5-ethyl- (CA INDEX NAME)

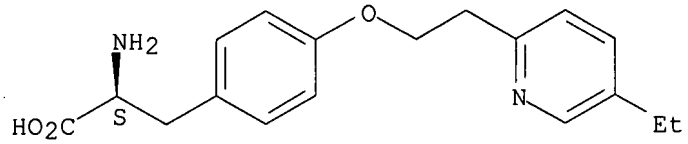


IT 795316-22-2P, O-[2-(5-Ethylpyridin-2-yl)ethyl]-DL-tyrosine
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(target intermediate; intermediate compound which is used for the preparation
of pioglitazone)
RN 795316-22-2 HCAPLUS
CN Tyrosine, O-[2-(5-ethyl-2-pyridinyl)ethyl]- (9CI) (CA INDEX NAME)



IT 794591-56-3P, O-[2-(5-Ethylpyridin-2-yl)ethyl]-L-tyrosine
795316-27-7P, O-[2-(5-Ethylpyridin-2-yl)ethyl]-D-tyrosine
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(target intermediate; intermediate compound which is used for the preparation
of pioglitazone)
RN 794591-56-3 HCAPLUS
CN L-Tyrosine, O-[2-(5-ethyl-2-pyridinyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

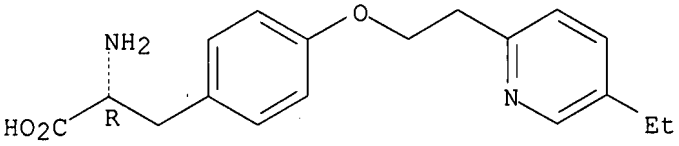


RN 795316-27-7 HCAPLUS

Updated Search

CN D-Tyrosine, O-[2-(5-ethyl-2-pyridinyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

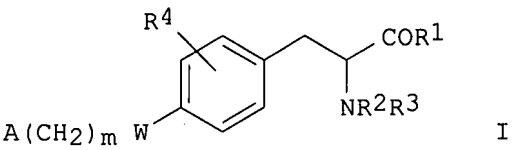


REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:77060 HCAPLUS
DOCUMENT NUMBER: 126:89361
TITLE: Preparation of (oxazolyl)alkoxyphenylpropionic acid derivatives as hypoglycemics and hypolipemics
INVENTOR(S): Takeno, Hidekazu; Ikemoto, Tomoyuki; Saitoh, Isao; Watanabe, Kazuhiro
PATENT ASSIGNEE(S): Sumitomo Metal Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9638415	A1	19961205	WO 1996-JP1380		19960524
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK					
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML					
JP 08325263	A	19961210	JP 1995-133460		19950531
AU 9657791	A	19961218	AU 1996-57791		19960524
PRIORITY APPLN. INFO.:			JP 1995-133460	A	19950531
			WO 1996-JP1380	W	19960524

OTHER SOURCE(S): MARPAT 126:89361
GI



I

AB The title compds. I [A represents a nitrogenous heterocycle; W represents oxygen or carbonyl; R1 represents hydroxy, an ester residue or a substituted imide group; and R2 and R3 represent each hydrogen, alkyl, aralkyl, alkanoyl, benzoyl, etc.; R4 = H, nitro, etc.; m = 0 - 2] are prepared The title compds. at 10 mg/kg gave 32 to 54% decrease of blood glucose in diabetic mice.
IT 185679-35-0P

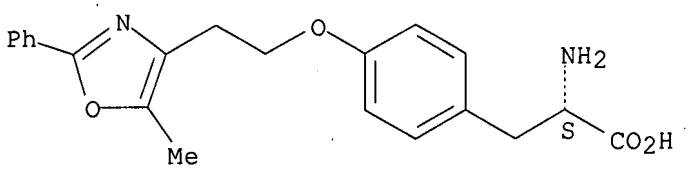
Updated Search

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of (oxazolyl)alkoxyphenylpropionic acid derivs. as hypoglycemics and hypolipemics)

RN 185679-35-0 HCAPLUS

CN L-Tyrosine, O-[2-(5-methyl-2-phenyl-4-oxazolyl)ethyl]- (9CI) (CA INDEX NAME)

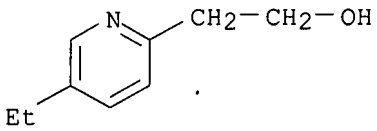
Absolute stereochemistry.



IT 5223-06-3, 2-(5-Ethyl-2-pyridyl)ethanol 72594-77-5
185679-62-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of (oxazolyl)alkoxyphenylpropionic acid derivs. as hypoglycemics and hypolipemics)

RN 5223-06-3 HCAPLUS

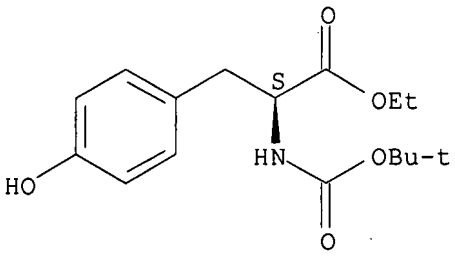
CN 2-Pyridineethanol, 5-ethyl- (CA INDEX NAME)



RN 72594-77-5 HCAPLUS

CN L-Tyrosine, N-[(1,1-dimethylethoxy)carbonyl]-, ethyl ester (CA INDEX NAME)

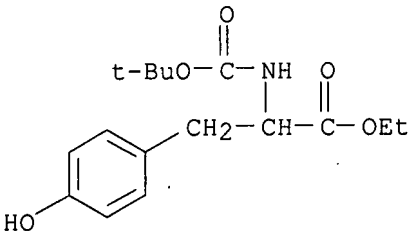
Absolute stereochemistry.



RN 185679-62-3 HCAPLUS

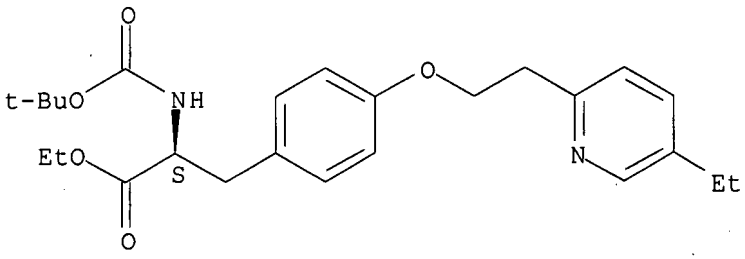
CN Tyrosine, N-[(1,1-dimethylethoxy)carbonyl]-, ethyl ester (9CI) (CA INDEX NAME)

Updated Search



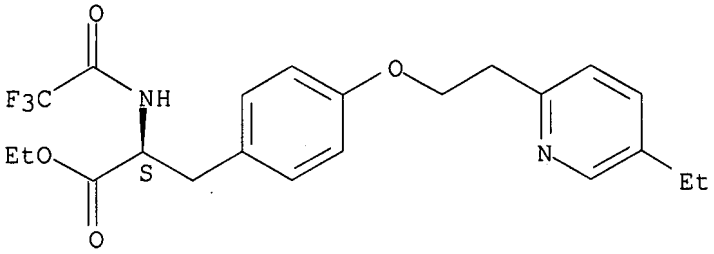
IT 185679-57-6P 185679-58-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of (oxazolyl)alkoxyphenylpropionic acid derivs. as hypoglycemics and hypolipemics)
RN 185679-57-6 HCAPLUS
CN L-Tyrosine, N-[(1,1-dimethylethoxy)carbonyl]-O-[2-(5-ethyl-2-pyridinyl)ethyl]-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 185679-58-7 HCAPLUS
CN L-Tyrosine, O-[2-(5-ethyl-2-pyridinyl)ethyl]-N-(trifluoroacetyl)-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> file caold

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	18.41	675.56
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-2.34	-15.60

FILE 'CAOLD' ENTERED AT 22:22:11 ON 24 SEP 2007

Updated Search

FILE COVERS 1907-1966
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE display formats.

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

=> d his

(FILE 'HOME' ENTERED AT 21:58:30 ON 24 SEP 2007)

FILE 'REGISTRY' ENTERED AT 21:58:36 ON 24 SEP 2007
L1 STRUCTURE UPLOADED
L2 2 S L1
L3 35 S L1 FULL

FILE 'HCAPLUS' ENTERED AT 22:03:28 ON 24 SEP 2007
L4 17 S L3
L5 0 S L4 AND CHUPAK, L?/AU
L6 0 S L4 AND BOYER, F?/AU
L7 0 S L4 AND HAGEN, S?/AU
L8 0 S L4 AND KANEKO, T?/AU
L9 0 S L4 AND LALL, M?/AU
L10 32 S 4 AND PETTERSSON, M?/AU
L11 0 S L4 AND LALL, M?/AU
L12 0 S L4 AND PETTERSSON, M?/AU
L13 0 S L4 AND PRASAD, J?/AU

FILE 'CAOLD' ENTERED AT 22:11:39 ON 24 SEP 2007
L14 0 S L3

FILE 'REGISTRY' ENTERED AT 22:11:45 ON 24 SEP 2007
L15 STRUCTURE UPLOADED
L16 50 S L15
L17 42185 S L16 FULL

FILE 'HCAPLUS' ENTERED AT 22:18:23 ON 24 SEP 2007
L18 5073 S L17/RCT
L19 10 S L18 AND L4

FILE 'REGISTRY' ENTERED AT 22:19:19 ON 24 SEP 2007
L20 STRUCTURE UPLOADED
L21 50 S L20
L22 46885 S L20 FULL

FILE 'HCAPLUS' ENTERED AT 22:21:33 ON 24 SEP 2007
L23 6111 S L22/RCT
L24 3 S L23 AND L19

Updated Search

```
     FILE 'CAOLD' ENTERED AT 22:22:11 ON 24 SEP 2007

=> s l22 and l17
          1210 L22
           581 L17
L25          0 L22 AND L17

=>

=> file reg
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         1.80     677.36

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)              SINCE FILE      TOTAL
                                                           ENTRY    SESSION
CA SUBSCRIBER PRICE                                         0.00     -15.60

FILE 'REGISTRY' ENTERED AT 22:24:21 ON 24 SEP 2007
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STRUCTURE FILE UPDATES:   23 SEP 2007  HIGHEST RN 947726-74-1
DICTIONARY FILE UPDATES:  23 SEP 2007  HIGHEST RN 947726-74-1

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TSCA INFORMATION NOW CURRENT THROUGH June 29, 2007

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=> e pioglitazone/cn
E1            1     PIOESTER 4248, POLYMER WITH 1,3,5-TRIS(OXIRANYLMETHYL)-1,3,5
                    -TRIAZINE-2,4,6(1H,3H,5H)-TRIONE/CN
E2            1     PIOESTER 4350-55/CN
E3            1 --> PIOGLITAZONE/CN
E4            1     PIOGLITAZONE 2-IMINE/CN
E5            1     PIOGLITAZONE HYDROCHLORIDE/CN
E6            1     PIOGLITAZONE N-OXIDE/CN
E7            1     PIOGLITAZONE NITRATE/CN
E8            1     PIOKTANIN/CN
E9            1     PIOLENE 1802/CN
E10           1     PIOLOFORM BL 16/CN
E11           1     PIOLOFORM BL 18/CN
E12           1     PIOLOFORM BL 24/CN

=> s e3
L26           1 PIOGLITAZONE/CN


Updated Search
```
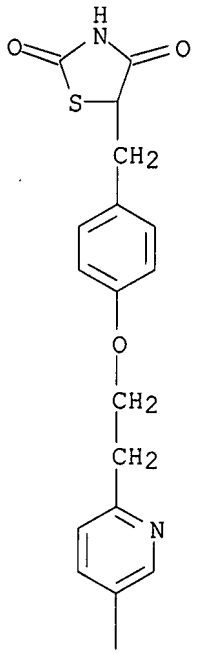

=> d l26

L26 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2007 ACS on STN
RN 111025-46-8 REGISTRY
ED Entered STN: 31 Oct 1987
CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-
(CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-
, (±)-
OTHER NAMES:
CN 5-[4-[2-(5-Ethyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione
CN Pioglitazone
CN U 72107
CN Zactos
DR 105355-27-9, 198077-89-3
MF C19 H20 N2 O3 S
CI COM
SR US Adopted Names Council (USAN)
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS,
BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, CSCHEM, DDFU,
DRUGU, EMBASE, HSDB*, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA,
MEDLINE, MRCK*, PATDPASPC, PHAR, PROMT, PROUSDDR, PS, RTECS*, SCISEARCH,
SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

PAGE 1-A



Updated Search

Et

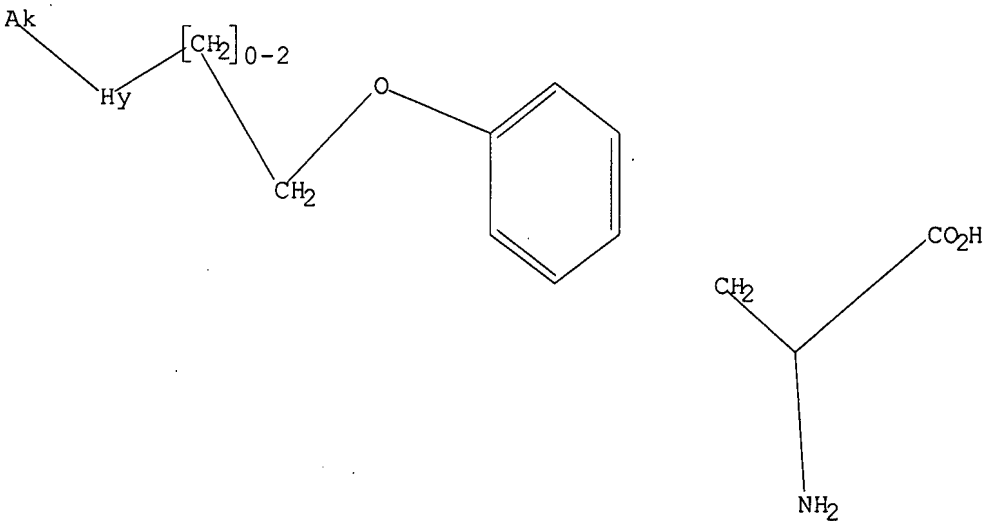
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1727 REFERENCES IN FILE CA (1907 TO DATE)
14 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1739 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=>
=>
Uploading C:\Documents and Settings\brobinson1\My Documents\stnweb\Queries\asdfadsm.str

L27 STRUCTURE UPLOADED

=> d l27
L27 HAS NO ANSWERS
L27 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l27
SAMPLE SEARCH INITIATED 22:46:09 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 6187 TO ITERATE

32.3% PROCESSED 2000 ITERATIONS 0 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 119024 TO 128456
PROJECTED ANSWERS: 0 TO 0

Updated Search

```
L28             0 SEA SSS SAM L27

=> s l27 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 171.65 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 22:46:14 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -   122592 TO ITERATE

100.0% PROCESSED   122592 ITERATIONS                                5 ANSWERS
SEARCH TIME: 00.00.02

L29             5 SEA SSS FUL L27

=> file hcaplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    195.20     872.56

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                      0.00     -15.60

FILE 'HCAPLUS' ENTERED AT 22:46:22 ON 24 SEP 2007
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FILE COVERS 1907 - 24 Sep 2007  VOL 147 ISS 14
FILE LAST UPDATED: 23 Sep 2007  (20070923/ED)

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 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s l29
L30             4 L29

=> s l29/rct
              4 L29
        3018046 RCT/RL
L31             2 L29/RCT
                  (L29 (L) RCT/RL)

=> file reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                      2.60     875.16

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
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Updated Search

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                                                      ENTRY    SESSION
CA SUBSCRIBER PRICE                                    0.00     -15.60

FILE 'REGISTRY' ENTERED AT 22:46:34 ON 24 SEP 2007
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STRUCTURE FILE UPDATES:   23 SEP 2007  HIGHEST RN 947726-74-1
DICTIONARY FILE UPDATES:  23 SEP 2007  HIGHEST RN 947726-74-1

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TSCA INFORMATION NOW CURRENT THROUGH June 29, 2007

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=>
Uploading C:\Documents and Settings\brobinson1\My Documents\stnweb\Queries\aqwe.str

L32     STRUCTURE UPLOADED

=> s l32
SAMPLE SEARCH INITIATED 22:51:41 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -      327 TO ITERATE

100.0% PROCESSED      327 ITERATIONS                                1 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          5456 TO     7624
PROJECTED ANSWERS:                1 TO       80

L33           1 SEA SSS SAM L32

=> s l32 full
THE ESTIMATED SEARCH COST FOR FILE 'REGISTRY' IS 171.65 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N or END:y
FULL SEARCH INITIATED 22:51:45 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -     6273 TO ITERATE

100.0% PROCESSED     6273 ITERATIONS                               70 ANSWERS
SEARCH TIME: 00.00.01

L34          70 SEA SSS FUL L32

=> file hcaplus
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION


Updated Search
```

```
FULL ESTIMATED COST                                    175.70    1050.86

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)       SINCE FILE      TOTAL
                                                      ENTRY    SESSION
CA SUBSCRIBER PRICE                                    0.00     -15.60

FILE 'HCAPLUS' ENTERED AT 22:51:50 ON 24 SEP 2007
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FILE COVERS 1907 - 24 Sep 2007  VOL 147 ISS 14
FILE LAST UPDATED: 23 Sep 2007  (20070923/ED)

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 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s l34
L35       1870 L34

=> s l33/prep
             1 L33
       4465713 PREP/RL
L36          0 L33/PREP
                 (L33 (L) PREP/RL)

=> s l34/prep
          1870 L34
       4465713 PREP/RL
L37          58 L34/PREP
                 (L34 (L) PREP/RL)

=> d his

     (FILE 'HOME' ENTERED AT 21:58:30 ON 24 SEP 2007)

     FILE 'REGISTRY' ENTERED AT 21:58:36 ON 24 SEP 2007
L1               STRUCTURE UPLOADED
L2             2 S L1
L3            35 S L1 FULL

     FILE 'HCAPLUS' ENTERED AT 22:03:28 ON 24 SEP 2007
L4            17 S L3
L5             0 S L4 AND CHUPAK, L?/AU
L6             0 S L4 AND BOYER, F?/AU
L7             0 S L4 AND HAGEN, S?/AU
L8             0 S L4 AND KANEKO, T?/AU
L9             0 S L4 AND LALL, M?/AU
```

Updated Search

```
L10          32 S 4 AND PETTERSSON, M?/AU
L11           0 S L4 AND LALL, M?/AU
L12           0 S L4 AND PETTERSSON, M?/AU
L13           0 S L4 AND PRASAD, J?/AU

     FILE 'CAOLD' ENTERED AT 22:11:39 ON 24 SEP 2007
L14           0 S L3

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L15             STRUCTURE UPLOADED
L16          50 S L15
L17       42185 S L16 FULL

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L18        5073 S L17/RCT
L19          10 S L18 AND L4

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L20             STRUCTURE UPLOADED
L21          50 S L20
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     FILE 'HCAPLUS' ENTERED AT 22:21:33 ON 24 SEP 2007
L23        6111 S L22/RCT
L24           3 S L23 AND L19

     FILE 'CAOLD' ENTERED AT 22:22:11 ON 24 SEP 2007
L25           0 S L22 AND L17

     FILE 'REGISTRY' ENTERED AT 22:24:21 ON 24 SEP 2007
                E PIOGLITAZONE/CN
L26           1 S E3
L27             STRUCTURE UPLOADED
L28           0 S L27
L29           5 S L27 FULL

     FILE 'HCAPLUS' ENTERED AT 22:46:22 ON 24 SEP 2007
L30           4 S L29
L31           2 S L29/RCT

     FILE 'REGISTRY' ENTERED AT 22:46:34 ON 24 SEP 2007
L32             STRUCTURE UPLOADED
L33           1 S L32
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     FILE 'HCAPLUS' ENTERED AT 22:51:50 ON 24 SEP 2007
L35        1870 S L34
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=> s l37 and l31
L38           2 L37 AND L31

=> d l38, ibib abs hitstr, 1-2

L38  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2004:1016040  HCAPLUS
DOCUMENT NUMBER:          141:424180
TITLE:                    Processes for making thiazolidinedione derivatives and
                          compounds thereof
INVENTOR(S):              Pospisilik, Karel; Zhu, Jie; Picha, Frantisek


Updated Search
```

PATENT ASSIGNEE(S): Synthon B.V., Neth.
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004101560	A1	20041125	WO 2004-EP5026	20040511
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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EP 1622898	A1	20060208	EP 2004-732115	20040511
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CN 1812988	A	20060802	CN 2004-80018359	20040511
JP 2007502847	T	20070215	JP 2006-529780	20040511

PRIORITY APPLN. INFO.: US 2003-469837P P 20030513
WO 2004-EP5026 W 20040511

OTHER SOURCE(S): MARPAT 141:424180
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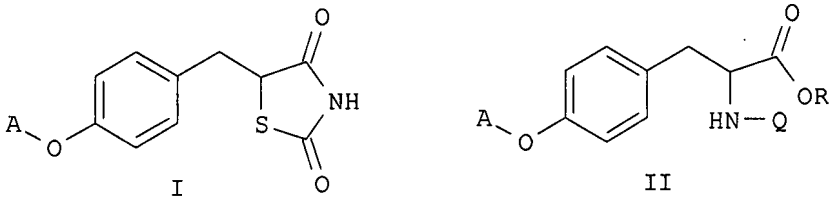


AB The invention relates processes for the synthesis of thiazolidinedione derivs. I (A is ethyl-2-pyridylethyl, [(2-pyridyl)methylamino]ethyl or [3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methyl] via reactions of amino acid intermediates II (same A, R is H or alkyl, Q is H or an amine-protecting group). The synthesis of pioglitazone is illustrated. Thus, 2-amino-3-[4-[2-(5-ethyl-2-pyridyl)ethoxy]phenyl]propionic acid, prepared by O-alkylation of L-tyrosine, underwent diazotization reaction to give the 2-bromo derivative which underwent cyclocondensation with thiourea to afford pioglitazone (isolated as the HCl salt).

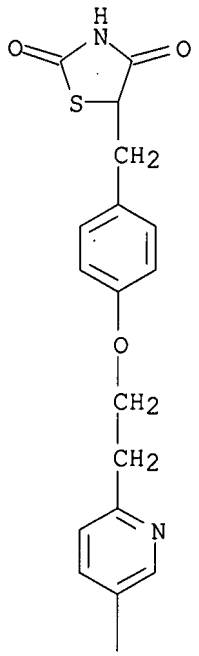
IT 111025-46-8P, Pioglitazone 112529-15-4P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(Processes for making thiazolidinedione derivs. and compds. thereof)

RN 111025-46-8 HCAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]- (CA INDEX NAME)

Updated Search

PAGE 1-A



PAGE 2-A

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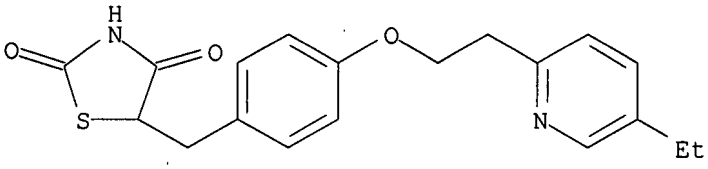
RN 112529-15-4 HCAPLUS
CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-, hydrochloride (1:1) (CA INDEX NAME)

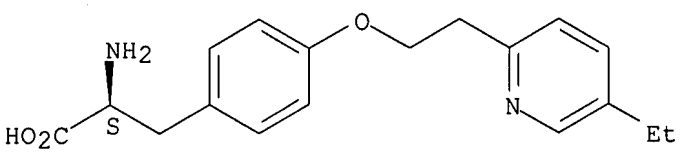


● HCl

IT 794591-56-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(Processes for making thiazolidinedione derivs. and compds. thereof)
RN 794591-56-3 HCAPLUS
CN L-Tyrosine, O-[2-(5-ethyl-2-pyridinyl)ethyl]- (9CI) (CA INDEX NAME)

Updated Search

Absolute stereochemistry.



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L38 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:996131 HCAPLUS
DOCUMENT NUMBER: 141:424428
TITLE: Intermediate compound, namely O-[2-(5-ethylpyridin-2-yl)ethyl]tyrosine, which is used for the preparation of the antidiabetic agent pioglitazone, and methods for its preparation and conversion to pioglitazone
INVENTOR(S): Duran, Lopez Ernesto
PATENT ASSIGNEE(S): Medichem, S.A., Spain
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Spanish
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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ES 2219180	B1	20060301		
CA 2525190	A1	20041118	CA 2004-2525190	20040504
EP 1623977	A1	20060208	EP 2004-731028	20040504
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US 2007083050	A1	20070412	US 2006-555659	20061219

PRIORITY APPLN. INFO.: ES 2003-1075 A 20030509
WO 2004-ES70031 W 20040504

OTHER SOURCE(S): CASREACT 141:424428; MARPAT 141:424428
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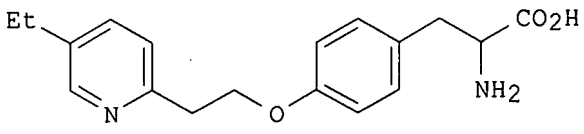
Updated Search



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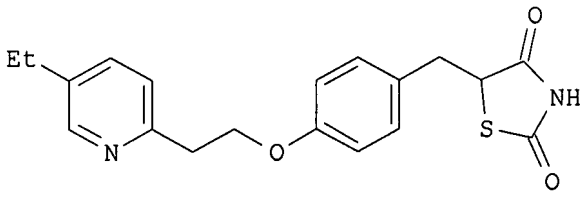

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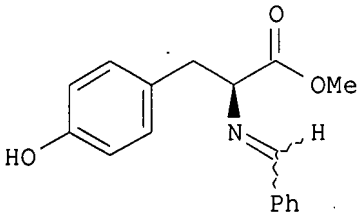

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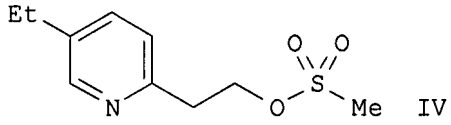


IV

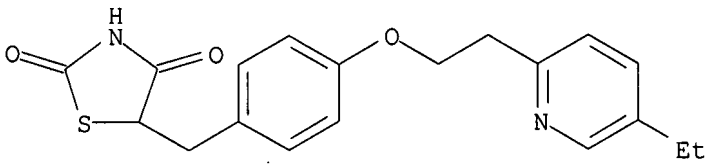
AB The invention relates to the novel O-substituted tyrosine derivative I, including pure or mixed enantiomers, racemates, salts, solvates, and hydrates. I and its stereoisomers and compds. are new key intermediates for the preparation of the antidiabetic agent pioglitazone (II). The invention also relates to a method of obtaining I from a natural product, L-tyrosine, in which the amino group, in the form of an aromatic imine group, is protected by an aldehyde or ketone. The invention further relates to a method of obtaining II from the intermediate compound I. The critical feature of the invention is protection of the tyrosine N-terminal as an imine, which allows etherification of the phenolic tyrosine OH group to occur without competing N-alkylation. Complete racemization during the process allows the more desirable racemic I to be prepared from the more readily available L-tyrosine. For instance, L-tyrosine was treated with SOCl2 in refluxing MeOH to give the Me ester, which was treated with PhCHO at room temperature in CH2Cl2 to give doubly protected tyrosine III. This phenolic compound was etherified with the mesylate IV (preparation given) using K2CO3 and Bu4N+Br- in PhMe at 70°, and the protected product was deprotected in situ first with acid (2N HCl) and then with base (50% NaOH), both at 70°, to give racemic I in 62.8% overall yield from L-tyrosine. Diazotization of the amino group in I in the presence of HBr gave the corresponding bromo compound, which was cyclized with thiourea to give the 2-imine derivative of II. Acid hydrolysis of the imine in refluxing aqueous HCl gave II in 40.7% yield from I. Four comparative processes for preparing I, using other standard amine protecting groups instead of a benzaldehyde imine, were examined Overall yields of I from L-tyrosine were 24.1% for Boc, 20.7% for Cbz, 11.5% for Ac, and poor (unisolated) for EtOCO, vs. 62.8% for benzylidene.

IT 112529-15-4P, Pioglitazone hydrochloride
RL: SPN (Synthetic preparation); PREP (Preparation)
(intermediate compound which is used for the preparation of pioglitazone)

RN 112529-15-4 HCAPLUS

Updated Search

CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-, hydrochloride (1:1) (CA INDEX NAME)

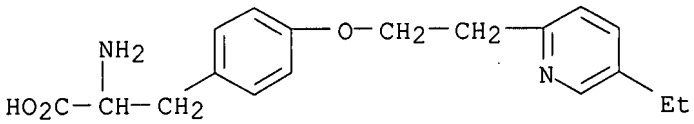


● HCl

IT 795316-22-2P, O-[2-(5-Ethylpyridin-2-yl)ethyl]-DL-tyrosine
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(target intermediate; intermediate compound which is used for the preparation of pioglitazone)

RN 795316-22-2 HCAPLUS

CN Tyrosine, O-[2-(5-ethyl-2-pyridinyl)ethyl]- (9CI) (CA INDEX NAME)

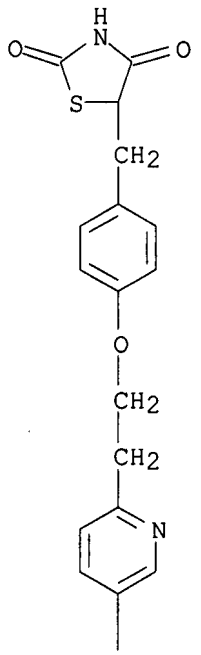


IT 111025-46-8P, Pioglitazone
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(target product; intermediate compound which is used for the preparation of pioglitazone)

RN 111025-46-8 HCAPLUS

CN 2,4-Thiazolidinedione, 5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]- (CA INDEX NAME)

Updated Search



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REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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FILE COVERS 1907-1966
FILE LAST UPDATED: 01 May 1997 (19970501/UP)

This file contains CAS Registry Numbers for easy and accurate substance identification. Title keywords, authors, patent assignees, and patent information, e.g., patent numbers, are now searchable from 1907-1966. TIFF images of CA abstracts printed between 1907-1966 are available in the PAGE

Updated Search

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  display formats.

  New CAS Information Use Policies, enter HELP USAGETERMS for details.

  This file supports REG1stRY for direct browsing and searching of
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L9           0 S L4 AND LALL, M?/AU
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     FILE 'REGISTRY' ENTERED AT 22:11:45 ON 24 SEP 2007
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L16         50 S L15
L17      42185 S L16 FULL

     FILE 'HCAPLUS' ENTERED AT 22:18:23 ON 24 SEP 2007
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L19         10 S L18 AND L4

     FILE 'REGISTRY' ENTERED AT 22:19:19 ON 24 SEP 2007
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L22      46885 S L20 FULL

     FILE 'HCAPLUS' ENTERED AT 22:21:33 ON 24 SEP 2007
L23       6111 S L22/RCT
L24          3 S L23 AND L19

     FILE 'CAOLD' ENTERED AT 22:22:11 ON 24 SEP 2007
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               E PIOGLITAZONE/CN
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L27            STRUCTURE UPLOADED
L28          0 S L27
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Updated Search
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     FILE 'REGISTRY' ENTERED AT 22:46:34 ON 24 SEP 2007
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     FILE 'HCAPLUS' ENTERED AT 22:51:50 ON 24 SEP 2007
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Field code qualifications can only be applied to text
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FILE CONTENT:1840 - 22 Sep 2007 VOL 147 ISS 14

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This file contains CAS Registry Numbers for easy and accurate substance
identification.
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PROJECTED ANSWERS:               0 TO        0

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L42  ANSWER 1 OF 1  CASREACT  COPYRIGHT 2007 ACS on STN
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TI   Intermediate compound, namely O-[2-(5-ethylpyridin-2-yl)ethyl]tyrosine,
     which is used for the preparation of the antidiabetic agent pioglitazone,
     and methods for its preparation and conversion to pioglitazone
IN   Duran, Lopez Ernesto
PA   Medichem, S.A., Spain
SO   PCT Int. Appl., 26 pp.
     CODEN: PIXXD2
DT   Patent
LA   Spanish
IC   ICM  C07D213-55
     ICS  C07D417-12; A61K031-44; A61P003-10
CC   34-2 (Amino Acids, Peptides, and Proteins)
     Section cross-reference(s): 27, 45
FAN.CNT 1
     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
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Updated Search
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OS MARPAT 141:424428

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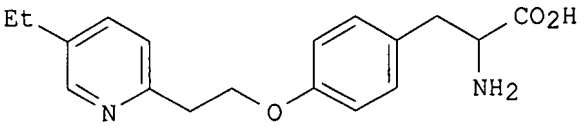

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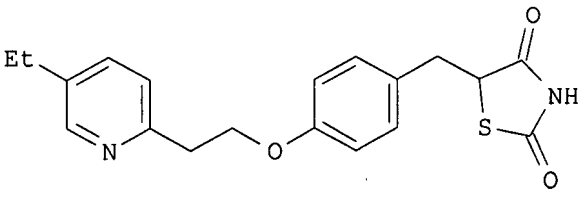
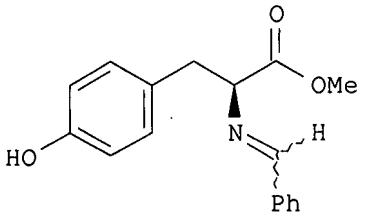
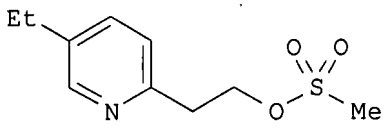


II



III



IV

AB The invention relates to the novel O-substituted tyrosine derivative I, including pure or mixed enantiomers, racemates, salts, solvates, and hydrates. I and its stereoisomers and compds. are new key intermediates for the preparation of the antidiabetic agent pioglitazone (II). The invention also relates to a method of obtaining I from a natural product, L-tyrosine, in which the amino group, in the form of an aromatic imine group, is protected by an aldehyde or ketone. The invention further relates to a method of obtaining II from the intermediate compound I. The critical feature of the invention is protection of the tyrosine N-terminal as an imine, which allows etherification of the phenolic tyrosine OH group to occur without competing N-alkylation. Complete racemization during the process allows the more desirable racemic I to be prepared from the more readily available L-tyrosine. For instance, L-tyrosine was treated with SOCl2 in refluxing MeOH to give the Me ester, which was treated with PhCHO at room temperature in CH2Cl2 to give doubly protected tyrosine III. This phenolic

Updated Search

compound was etherified with the mesylate IV (preparation given) using K2CO3 and Bu4N+Br- in PhMe at 70°, and the protected product was deprotected in situ first with acid (2N HCl) and then with base (50% NaOH), both at 70°, to give racemic I in 62.8% overall yield from L-tyrosine. Diazotization of the amino group in I in the presence of HBr gave the corresponding bromo compound, which was cyclized with thiourea to give the 2-imine derivative of II. Acid hydrolysis of the imine in refluxing aqueous HCl gave II in 40.7% yield from I. Four comparative processes for preparing I, using other standard amine protecting groups instead of a benzaldehyde imine, were examined Overall yields of I from L-tyrosine were 24.1% for Boc, 20.7% for Cbz, 11.5% for Ac, and poor (unisolated) for EtOCO, vs. 62.8% for benzylidene.

ST ethylpyridinylethyltyrosine prepn intermediate pioglitazone antidiabetic; etherification imine protected tyrosine ester ethylpyridinylethyl mesylate

IT Antidiabetic agents
(intermediate compound which is used for the preparation of pioglitazone)

IT Amino acids, preparation
Schiff bases
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate compound which is used for the preparation of pioglitazone)

IT Etherification
Protective groups
(preparation of [(ethylpyridinyl)ethyl]tyrosine via etherification of imine-protected tyrosine and use as intermediate for pioglitazone)

IT 2440-79-1P, N-Acetyl-L-tyrosine methyl ester 4326-36-7P, N-Boc-L-tyrosine methyl ester 13512-31-7P, N-Cbz-L-tyrosine methyl ester 215596-38-6P, N-(Ethoxycarbonyl)-L-tyrosine methyl ester 795316-23-3P, N-Boc-O-[2-(5-ethylpyridin-2-yl)ethyl]-L-tyrosine methyl ester 795316-24-4P, N-Boc-O-[2-(5-ethylpyridin-2-yl)ethyl]-L-tyrosine 795316-25-5P, O-[2-(5-Ethylpyridin-2-yl)ethyl]-L-tyrosine methyl ester 795316-26-6P, N-Cbz-O-[2-(5-ethylpyridin-2-yl)ethyl]-L-tyrosine methyl ester
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(comparison process intermediate; intermediate compound which is used for the preparation of pioglitazone)

IT 75-36-5, Acetyl chloride 501-53-1, Benzyl chloroformate 541-41-3, Ethyl chloroformate 24424-99-5, Di-tert-butyl dicarbonate
RL: RCT (Reactant); RACT (Reactant or reagent)
(comparison protecting agent; intermediate compound which is used for the preparation of pioglitazone)

IT 3417-91-2, L-Tyrosine methyl ester hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(comparison starting material; intermediate compound which is used for the preparation of pioglitazone)

IT 112529-15-4P, Pioglitazone hydrochloride
RL: SPN (Synthetic preparation); PREP (Preparation)
(intermediate compound which is used for the preparation of pioglitazone)

IT 1080-06-4P, L-Tyrosine methyl ester 69955-04-0P, N-Benzylidene-L-tyrosine methyl ester 105355-26-8P, Pioglitazone 2-imine 144809-26-7P, 2-(5-Ethylpyridin-2-yl)ethyl methanesulfonate 674798-32-4P, α-Bromo-4-[2-(5-ethylpyridin-2-yl)ethoxy]benzenepropanoic acid 795316-28-8P, N-Benzylidene-O-[2-(5-ethylpyridin-2-yl)ethyl]-L-tyrosine methyl ester
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process intermediate; intermediate compound which is used for the preparation

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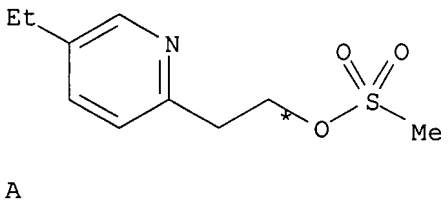
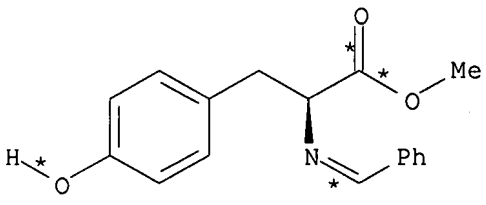
of pioglitazone)
IT 100-52-7, Benzaldehyde, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(protecting agent; intermediate compound which is used for the preparation of
pioglitazone)
IT 60-18-4, L-Tyrosine, reactions 62-56-6, Thiourea, reactions 124-63-0, Methanesulfonyl chloride 5223-06-3, 2-(5-Ethylpyridin-2-yl)ethanol
RL: RCT (Reactant); RACT (Reactant or reagent)
(starting material; intermediate compound which is used for the preparation of
pioglitazone)
IT 795316-22-2P, O-[2-(5-Ethylpyridin-2-yl)ethyl]-DL-tyrosine
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(target intermediate; intermediate compound which is used for the preparation
of pioglitazone)
IT 794591-56-3P, O-[2-(5-Ethylpyridin-2-yl)ethyl]-L-tyrosine 795316-27-7P, O-[2-(5-Ethylpyridin-2-yl)ethyl]-D-tyrosine
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(target intermediate; intermediate compound which is used for the preparation
of pioglitazone)
IT 111025-46-8P, Pioglitazone
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(target product; intermediate compound which is used for the preparation of pioglitazone)
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Leciva, A; WO 2002088120 A1 2002 CAPLUS
(2) Meguro, K; US 4687777 A 1987 CAPLUS
(3) Sumitomo Metal Ind Ltd; JP 08-325263 A 1996 CAPLUS
(4) Sumitomo Metal Ind Ltd; http://www4.ipdl.jpo.go.jp/Tokujitu/PAJdetail.ipdl?N0000=60&N0120=01&N2001=2&N3001=H08-325263 1996
(5) Welfide Kk; JP 2000344748 A 2000 CAPLUS

RX(1) OF 80 ...A + B ===> C...



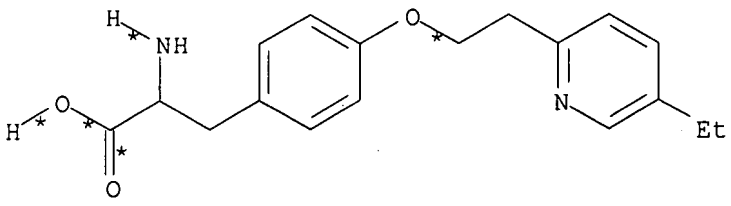
A



B

Updated Search

(1) →



C

RX(1) RCT A 144809-26-7

STAGE(1)
SOL 108-88-3 PhMe

STAGE(2)
RGT D 584-08-7 K2CO3
CAT 1643-19-2 Bu4N.Br

STAGE(3)
RCT B 69955-04-0

STAGE(4)
SOL 108-88-3 PhMe

STAGE(5)
RGT D 584-08-7 K2CO3

STAGE(6)
CAT 1643-19-2 Bu4N.Br

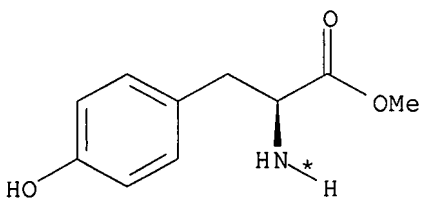
STAGE(7)
RGT E 7647-01-0 HCl
SOL 7732-18-5 Water

STAGE(8)
RGT F 1310-73-2 NaOH
SOL 7732-18-5 Water

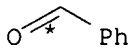
STAGE(9)
RGT E 7647-01-0 HCl
SOL 7732-18-5 Water

PRO C 795316-22-2
NTE last stage neutralization

RX(2) OF 80 ...J + K ===> B...



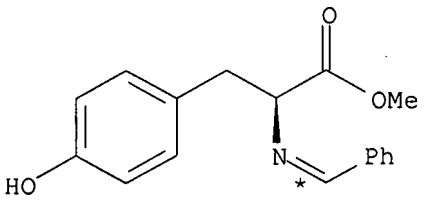
J



K

(2) →

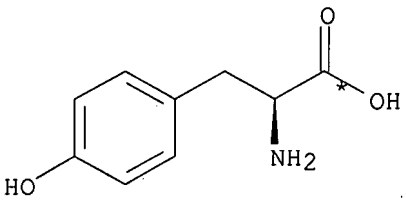
Updated Search



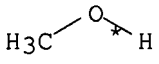
B

RX(2) RCT J 1080-06-4, K 100-52-7
PRO B 69955-04-0
SOL 75-09-2 CH2Cl2
CON overnight, room temperature

RX(3) OF 80 M + N ===> J...

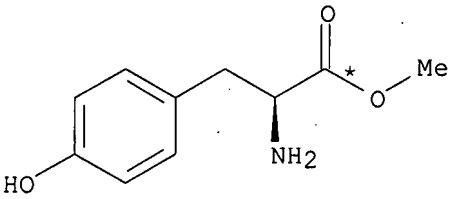


M



N

(3)



J
YIELD 100%

RX(3) RCT M 60-18-4, N 67-56-1

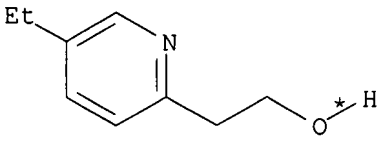
STAGE(1)
SOL 67-56-1 MeOH
CON room temperature -> 0 deg C

STAGE(2)
RGT O 7719-09-7 SOCl2
CON SUBSTAGE(1) 20 minutes, 0 deg C
SUBSTAGE(2) 0 deg C -> room temperature
SUBSTAGE(3) room temperature -> reflux
SUBSTAGE(4) 4.5 hours, reflux

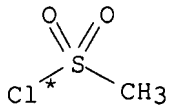
PRO J 1080-06-4

Updated Search

RX(4) OF 80 P + Q ===> A...

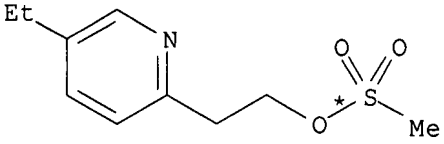


P



Q

(4) →



A

RX(4) RCT P 5223-06-3

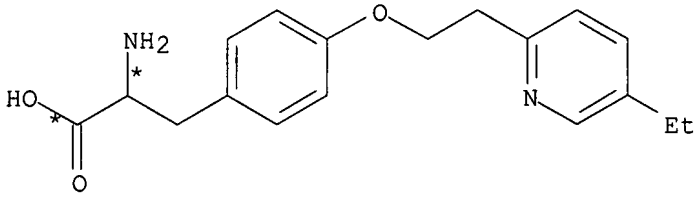
STAGE(1)
SOL 108-88-3 PhMe
CON room temperature

STAGE(2)
RGT R 121-44-8 Et3N
CON room temperature -> 0 deg C

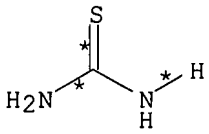
STAGE(3)
RCT Q 124-63-0
CON SUBSTAGE(1) 75 minutes, 0 - 10 deg C
SUBSTAGE(2) 10 deg C -> room temperature
SUBSTAGE(3) 1 hour, room temperature

PRO A 144809-26-7

RX(5) OF 80 ...C + S ===> T



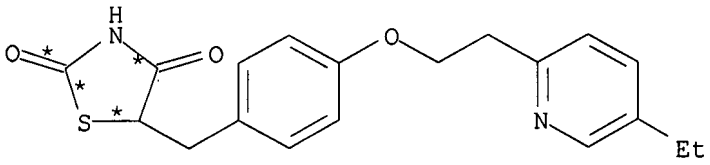
C



S

(5) →

Updated Search



T
YIELD 41%

RX(5) RCT C 795316-22-2

STAGE(1)
SOL 7732-18-5 Water

STAGE(2)
RGT U 10035-10-6 HBr
SOL 7732-18-5 Water

STAGE(3)
RGT V 7632-00-0 NaNO2
SOL 7732-18-5 Water

STAGE(4)
SOL 75-09-2 CH2Cl2

STAGE(5)
RCT S 62-56-6
RGT W 127-09-3 AcONa

STAGE(6)
SOL 64-17-5 EtOH

STAGE(7)
RGT X 144-55-8 NaHCO3
SOL 7732-18-5 Water, 141-78-6 AcOEt

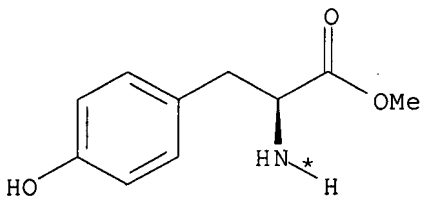
STAGE(8)
RGT E 7647-01-0 HCl
SOL 7732-18-5 Water

STAGE(9)
RGT F 1310-73-2 NaOH
SOL 7732-18-5 Water

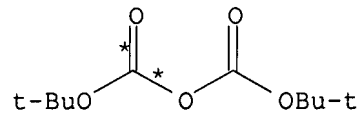
PRO T 111025-46-8
NTE key step; last stage neutralization

RX(6) OF 80 ...J + AA ===> AB...

Updated Search

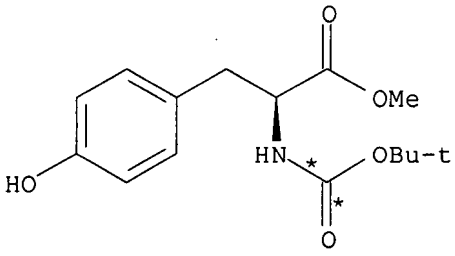


J



AA

(6) →



AB
YIELD 90%

RX(6) RCT J 1080-06-4

STAGE(1)
SOL 75-09-2 CH2Cl2

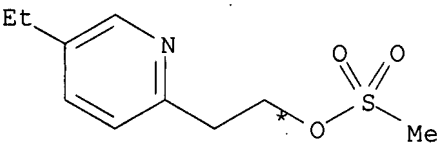
STAGE(2)
RGT R 121-44-8 Et3N

STAGE(3)
RCT AA 24424-99-5
SOL 75-09-2 CH2Cl2

STAGE(4)
SOL 7732-18-5 Water

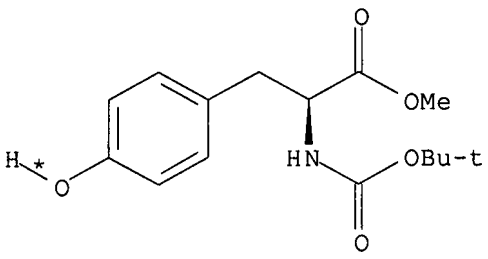
PRO AB 4326-36-7
NTE last stage quench

RX(7) OF 80 ...A + AB ===> AC...



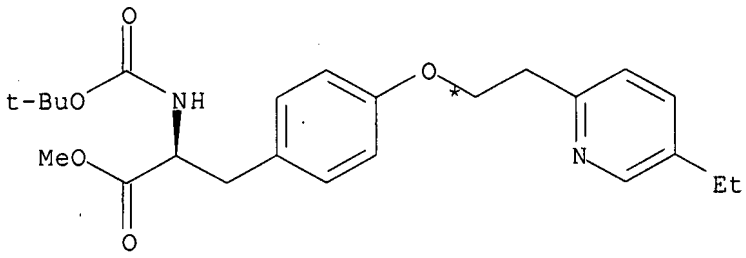
A

Updated Search



AB

(7)



AC

RX(7) RCT A 144809-26-7, AB 4326-36-7

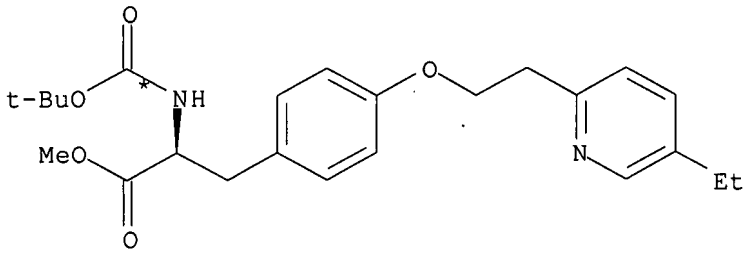
STAGE(1)
SOL 108-88-3 PhMe

STAGE(2)
RGT D 584-08-7 K2CO3

STAGE(3)
SOL 67-56-1 MeOH, 108-88-3 PhMe

PRO AC 795316-23-3

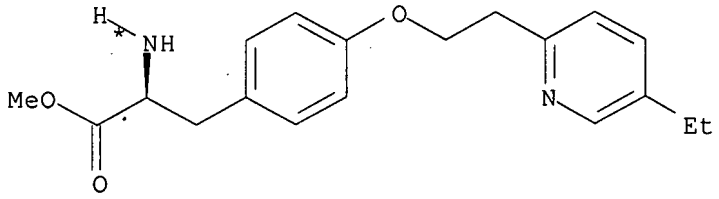
RX(8) OF 80 ...AC ===> AD...



AC

(8)

Updated Search



AD
YIELD 42%

RX(8) RCT AC 795316-23-3

STAGE(1)

STAGE(2)
RGT AE 1310-58-3 KOH
SOL 7732-18-5 Water, 67-56-1 MeOH

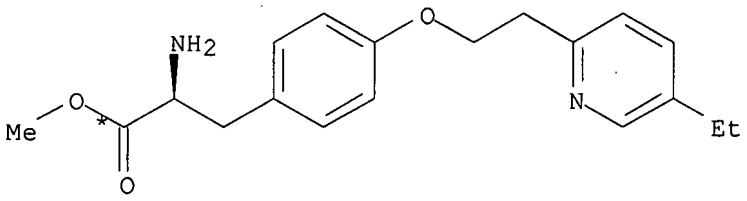
STAGE(3)
SOL 67-56-1 MeOH

STAGE(4)
RGT O 7719-09-7 SOCl2

STAGE(5)
RGT X 144-55-8 NaHCO3
SOL 7732-18-5 Water

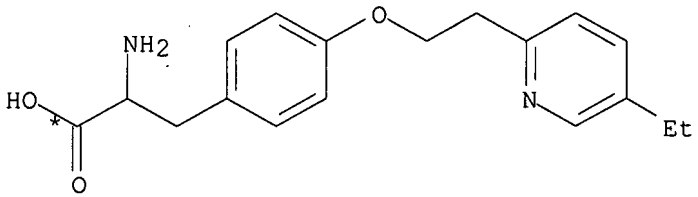
PRO AD 795316-25-5

RX(9) OF 80 ...AD ===> C...



AD

(9) ⟶



C
YIELD 63%

Updated Search

RX(9) RCT AD 795316-25-5

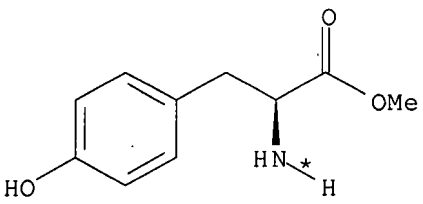
STAGE(1)
SOL 7732-18-5 Water, 67-56-1 MeOH

STAGE(2)
RGT AE 1310-58-3 KOH

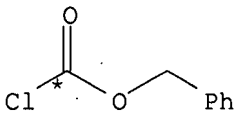
STAGE(3)
RGT E 7647-01-0 HCl
SOL 7732-18-5 Water

PRO C 795316-22-2
NTE last stage neutralization

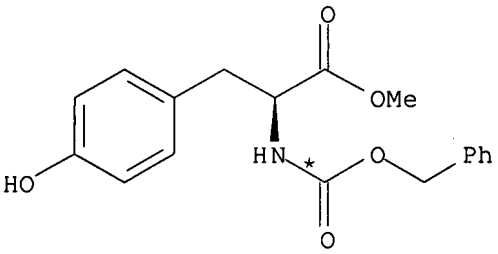
RX(10) OF 80 AF + AG ===> AH...



● HCl



AF AG (10) →



AH
YIELD 92%

RX(10) RCT AF 3417-91-2

STAGE(1)

STAGE(2)
RGT D 584-08-7 K2CO3

STAGE(3)
SOL 7732-18-5 Water, 67-64-1 Me2CO

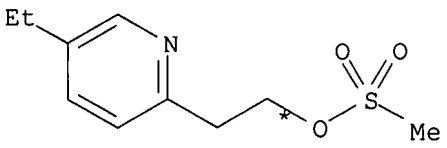
Updated Search

STAGE(4)
RCT AG 501-53-1

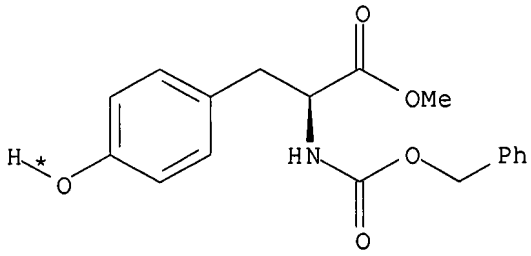
STAGE(5)
SOL 141-78-6 AcOEt

PRO AH 13512-31-7

RX(11) OF 80 ...A + AH ===> AJ...

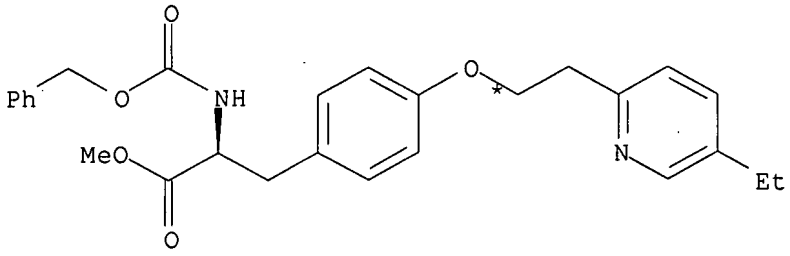


A



AH

(11)



AJ

RX(11) RCT A 144809-26-7, AH 13512-31-7

STAGE(1)
SOL 108-88-3 PhMe

STAGE(2)
RGT D 584-08-7 K2CO3

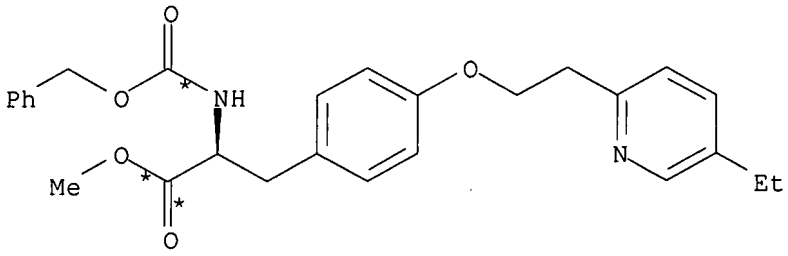
STAGE(3)
SOL 108-21-4 Acetic acid, 1-methylethyl ester

STAGE(4)
CAT 1643-19-2 Bu4N.Br

PRO AJ 795316-26-6

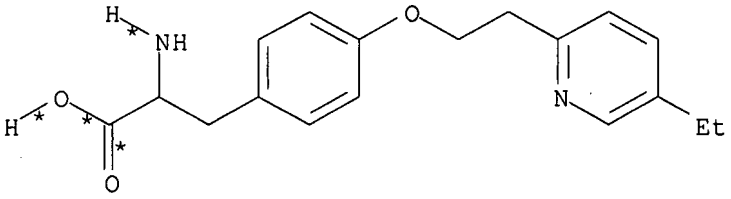
Updated Search

RX(12) OF 80 ...AJ ===> C...



AJ

(12)



C
YIELD 22%

RX(12) RCT AJ 795316-26-6

STAGE(1)
SOL 67-56-1 MeOH

STAGE(2)
RGT F 1310-73-2 NaOH
SOL 7732-18-5 Water

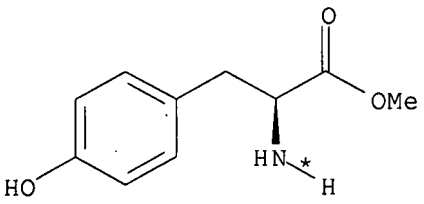
STAGE(3)
RGT E 7647-01-0 HCl
SOL 7732-18-5 Water

STAGE(4)
RGT F 1310-73-2 NaOH
SOL 7732-18-5 Water

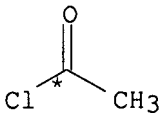
PRO C 795316-22-2
NTE last stage neutralization

RX(13) OF 80 ...J + AL ===> AM...

Updated Search

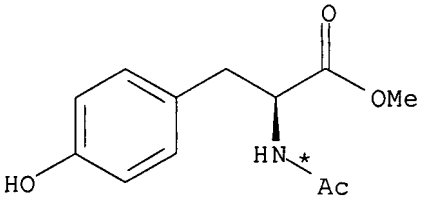


J



AL

(13)



AM
YIELD 85%

RX(13) RCT J 1080-06-4

STAGE(1)

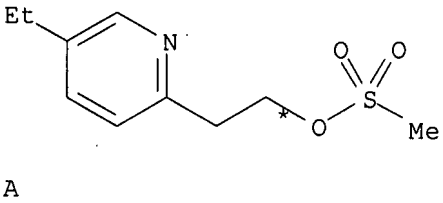
STAGE(2)
RGT AN 497-19-8 Na2CO3

STAGE(3)
SOL 7732-18-5 Water, 75-09-2 CH2Cl2

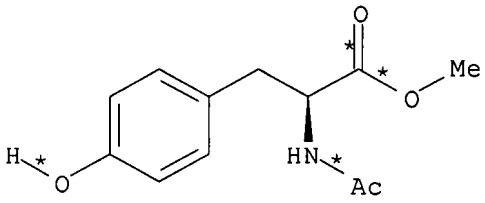
STAGE(4)
RCT AL 75-36-5

PRO AM 2440-79-1

RX(14) OF 80 ...A + AM ===> C...



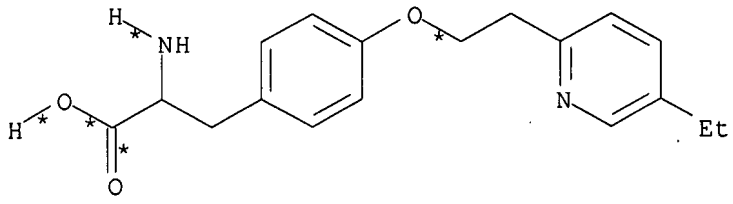
A



AM

Updated Search

(14) →



C
YIELD 14%

RX(14) RCT A 144809-26-7, AM 2440-79-1

STAGE(1)

STAGE(2)
RGT D 584-08-7 K2CO3
CAT 1643-19-2 Bu4N.Br

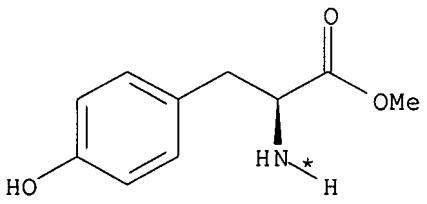
STAGE(3)
SOL 108-88-3 PhMe

STAGE(4)
RGT F 1310-73-2 NaOH
SOL 7732-18-5 Water

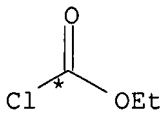
STAGE(5)
RGT E 7647-01-0 HCl
SOL 7732-18-5 Water

PRO C 795316-22-2
NTE last stage neutralization

RX(15) OF 80 ...J + AO ===> AP



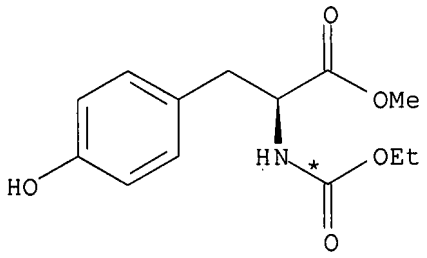
J



AO

(15) →

Updated Search



AP
YIELD 98%

RX(15) RCT J 1080-06-4

STAGE(1)

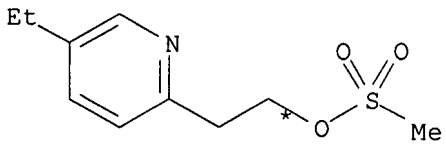
STAGE(2)
RGT D 584-08-7 K2CO3

STAGE(3)
SOL 7732-18-5 Water, 67-64-1 Me2CO

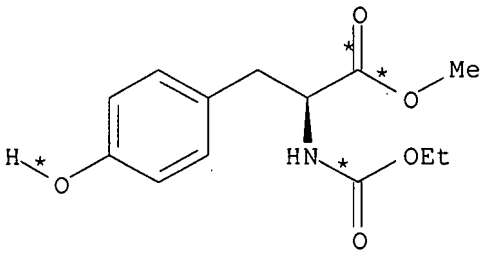
STAGE(4)
RCT AO 541-41-3

PRO AP 215596-38-6

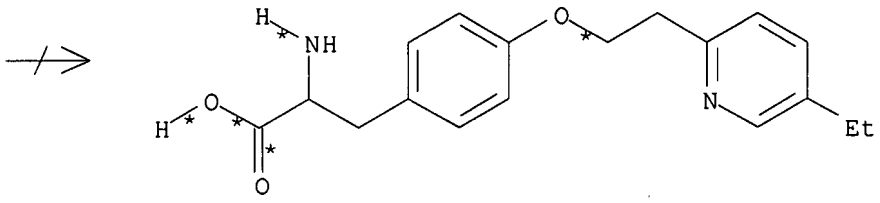
RX(16) OF 80 A + AP =/=> C



A



AP



C

RX(16) RCT A 144809-26-7, AP 215596-38-6

Updated Search

STAGE(1)

STAGE(2)
RGT D 584-08-7 K2CO3

STAGE(3)
SOL 108-21-4 Acetic acid, 1-methylethyl ester

STAGE(4)
SOL 7732-18-5 Water

STAGE(5)
RGT E 7647-01-0 HCl
SOL 7732-18-5 Water

PRO C 795316-22-2
NTE failed reaction